The Urinary Function of the Kidney

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GRUNE & STRATTON, INC.
New York 1950

Grune & Stratton, Inc.
381 Fourth Avenue
New York 16, New York

Printed in the United States of America
by Boyd Printing Co., Inc., Albany, N. Y.

Bound by H. Wolff Book Mfg. Co., Inc.
in water repellent pyroxylin impregnated cloth

To

EDWARD FREDERICK ADOLPH

revered teacher

Acknowledgments

My sincere thanks are due all those who helped in the completion of this book. I should like to express my thanks to numerous colleagues who were so cooperative in allowing me to use certain of their materials

To the following publishers, who granted permission for the use of certain figures and tables to which they hold copyrights, I give grateful acknowledgment:

J. & A Churchill Ltd., London; Interscience Publishers, Inc, New York; Paul B. Hoeber, Inc., New York, Longmans Green & Co., Ltd, London; McGraw-Hill Book Company, Inc, New York; Oxford University Press, Inc., New York, the Ronald Press Company, New York; Charles C Thomas, Springfield, Ill, Williams & Wilkins Co, Baltimore, The Year Book Publishers, Inc., Chicago.

In addition I would like to thank the following journals whose pages were the source of other data:

American Journal of the Medical Sciences; American Journal of Physiology, Annals of Internal Medicine, Journal of Clinical Investigation; Journal of Experimental Medicine; The Lancet; Proceedings of the Royal Society (London).

Full information about these sources is given in the Bibliography, to which reference is made at appropriate places in the text

A. V. W.

Contents

Foreword

By making available this informative and thought-provoking book, my colleague, Dr A V. Wolf, has performed a brilliant and timely service to those who wish to keep abreast of the developments in renal physiology and related fields Many investigators and clinicians are dissatisfied today with questionable hypotheses that have gained widespread acceptance, largely through a process of repetition They will welcome the opportunity to revise outmoded concepts regarding body fluid and electrolyte metabolism in health and disease.

Dr. Wolf draws from his own extensive background as investigator and teacher and from the abundant literature on the subject His original integration of established facts, old and new, advances the reader's ability to understand variations in volume and composition of urine under different conditions The quantitative view stressed by the author is of great import, it is particularly practical in the treatment of the problems of thirst, diuresis, and steady states Dr Wolf has keen insight into the needs of the physiologist, the clinician, and the pharmacologist He clarifies such intricate subjects as the regulation of body volumes as compared to body concentrations; the problems of absolute and relative dehydration and hydration; renal regulations, and the endocrine relationship to urine volume and composition His classification of edemas should gain universal acceptance

Many, like myself, will appreciate the author's singling out of commonly employed terms that are ambiguous or meaningless and his efforts to replace them with logical and exact expressions. This example in semantics might well be heeded by those who plan reviews of other topics in the biological sciences

The monograph is documented with the most extensive bibliography thus far published in this field, its value to the investigator is obvious I was pleasantly impressed by the arrangement and structure of the book Text and illustrations are well balanced and there is a useful system of cross references.

I consider myself privileged to have been called upon to introduce Dr. Wolf's "The Urinary Function of the Kidney." It is a much needed, refreshing review, a book that seems destined to achieve the status of a classic

HAROLD C WIGGERS, PH.D

Albany, N. Y
May, 1950

Preface

THE experimental partitioning of glomerular and tubular functions which has appeared feasible in recent years, and which depends upon the behavior of substances supposed to be susceptible of unique renal processing, has led to a characteristic pattern of thinking about renal function. In this pattern, renal excretion is conceived at once in terms of that euphonious synonym, *clearance*, and in terms of the more obvious anatomy and topology of the kidney. Many see in this the substantial basis for a modern theoretic physiology, forthright in its methods and happily attractive to the analytically minded.

There is another pattern of thinking which differs in that it emphasizes regulation rather than excretion. It is described here as the urinary function of the kidney. Those who share this view do not imagine it is the final aim of the kidney to "clear" things, nor do they sound other insistent notes of orthodoxy. In the regulatory view, excretion is only one thermodynamic facet of the total effort of the kidney. The urine is regarded as a physiologic unit, sui generis, whose formation and removal permit the body to maintain its substance and volume in the face of continuous and varying activity of other emunctories, and of paths of intake. Thus, what the kidneys do represents the difference between what must be done to maintain normal living states and what is being done to this end by all extrarenal activities.

Basically, the two concepts deal with the same problems but, for example, where the concept of clearance stresses the independence of separate excretory systems for substances like water, sodium, and bicarbonate, the concept of regulation stresses an interdependence in varying degrees between these systems. Little has been done so far to harmonize the differences between these two views. One trouble seems to be that renal physiology suffers from a paucity of facts which have meaning for other fields. It is partly in this regard that I have tried to integrate aspects of renal function, water balance, and electrolyte metabolism in ways which seem to me instructive or provocative. If there seems to be an untoward preoccupation with the vicissitudes of urinary flow it comes not simply by predilection but by way of the desire to bring into some order an agglomerate of information which has been long neglected for the more glamorous fields of renal physiology.

ening discussions of urinary physics; to Marion F. Dondale and Helen A. Fraser, librarians of the Albany Medical College Library, who caused the accumulation of reference material to appear almost painless, to Charles H Tracy, for adapting so many diagrams as figures for this book; and to my wife, Orietta, who helped to make whatever is, scrupulous.

Financial support from the U. S. Public Health Service made possible the original research reported here on fluid transfers among interstitial compartments and the function of the plasma as a conductor of fluid. Grants from the Dazian Foundation for Medical Research (which supported in 1945–1946 much of the work reported here and elsewhere, and which has come generously to my aid once again), from the Winthrop Research Fund of the Albany Medical College, and from the Department of Physiology and Pharmacology of the Albany Medical College defrayed part of the cost of publishing this book

A V Wolf, Ph D.

Albany, New York
May, 1950

It is difficult for me to avoid some mention of the curious multiplicity of hypotheses which afflicts renal physiology, since it is my belief *that few deserve consideration for having breadth.* Except for some few detached scientists, most investigators usually observe only what their minds are prepared to observe, and dwell on those facts which best fit their ideas, to the exclusion of others. The effect has been to engender perennial oversimplifications. Too many delude themselves that their experiments have demonstrated this or that functional relation, and lack of space in our scientific journals appears to protect hypotheses from suffering sustained and calculated attack.

Viewed historically, hypothesizing about the kidney seems to have little more validity for having stemmed from authority. Certain important critical views of even learned renal physiologists are unimpressive in retrospect. Much has been said, for example, of the too great defensive strength of an old "secretion" theory and we were once cautioned to take no refuge there until the resources of a "reabsorption" theory were exhausted. But what flights of fancy were sustained along with the stubbornly persistent belief in the latter theory at a time when it was manifestly at odds with sober evidence Investigators still feel impelled to generate appealing hypotheses concerning the precise measurement of glomerular filtration, renal water conservation, or the independence of tubular reabsorptive processes even though these ideas are contingent and possibly unverifiable Fortunately, they have just enough substance to stimulate further research

No special hypothesis, much less theory, of renal function is proposed in this book If it tells the reader that, in the writer's opinion, clearance analysis is, in general, as empirical as other analysis and that the illusion to the contrary is the dry rot of modern renal physiology, it nevertheless treats these differing contentions side by side. The writer admits freely that he does not always know when he is rationalizing his own persuasions, or applying without warrant his limited experience, or otherwise indulging the Idols of the Cave. In consequence (and not by perversity alone) the following pages are occasionally agnostic where to others the physiological faith seems clear.

It is a pleasure to declare here my indebtedness to some of those who helped to fructify this work—to Dr. Harold C Wiggers, Professor of Physiology and Pharmacology of the Albany Medical College, for his warm and effective encouragement; to Agnes E Mullin and Wilma Whitney, faithful technicians who have contributed to the original researches reported herein and to dreary tasks of checking references and other bookish things; to Dr. Herta R. Leng, Associate Professor of Physics of the Rensselaer Polytechnic Institute, for enlight-

CHAPTER I

The Urinary Function in Water Balance and Fluid Transfer

1 1 One of the useful abstractions of theoretic physiology is the balance concept Perhaps the simplest definition of a balance is the expression

$$\text{Balance} = \text{Gain} - \text{Loss}$$

An organism in balance is defined as one that maintains constant, within measured limits, the contents of one or more specified body components[16] In practice a state of balance must be defined arbitrarily except under unusual experimental conditions Intakes (gains) are not physiologically constant or uninterrupted, neither are outputs (losses) We often call the "normal" or the usual state one of balance, that is, *zero* balance, and we choose elapsed intervals of observation so that in the normal state the balance formula equates to zero If, in this chosen interval, intake (and, therefore, rate of intake) is greater than output (or rate of output), the balance is called positive When output exceeds intake, then conversely, the balance is called negative. In mammals, intake is usually intermittent and output continuous The usual balance obtains when neither intake nor output is forced, when there is neither privation nor manipulative procedure, and where sufficiently long periods (usually 24 hours) elapse so that rhythms of feeding and sleeping shall be minimized

Zero balance is a critical equilibration point With respect to water a man comes into zero balance at meal times, when we suppose he has no excesses or deficits (positive or negative loads, respectively) If he then loads himself with water by forced ingestion or infusion, regulatory mechanisms come into play to reduce the water load to zero In the absence of excessive sweating, the reduction of a large positive water load is usually, and mainly, accomplished through renal action, that is, urinary flow augments A negative load of water or absolute dehydration usually calls forth a compensatory mechanism in the form of reduced urine flow which favors the restoration of water balance by decreasing the difference between intake and output

surface area, that is, is proportional to metabolic rate and surface area rather than body weight However, Adolph[16, 19] finds, for mammals varying in size from elephant to mouse, that the rate of water intake varies with the 0 88 power of the body weight, the heterogonic equation being

$$i = 0\,010B^{0\,88} \quad (1)$$

where i is rate of water intake in grams per hour and B is body weight in grams

In a hot, desert environment the facultative water output of the skin in the form of sweat may amount to several liters daily[20]. Similar water loss through the feces occurs in diarrhea. In these instances a water balance can be struck through appropriate adjustments in the intakes, chiefly by drink which is obligated in larger quantities. Clinically it becomes difficult to manage the water balance account of an individual as his condition deviates from the physiological normal, especially where the extent of the excess or deficit is not well known or the magnitude of output is not accurately gaged For example, in most fevers no sweat is produced in the early stages in spite of a considerable rise in body temperature[629] whereas profuse sweating is a regular symptom of the defervescent stage In hyperthermia the basal metabolic rate increases about 13 per cent per degree C A rough approximation, based on a water loss of one cc. per Calorie, suggests an increased loss of 13 per cent more water per degree C. of fever The proportionality between energy metabolism and insensible loss has been reviewed by Peters[841] The physiology of balance suggests for therapy that we create small positive water loads to cover deficits beyond the immediate requirements, and so long as mechanisms of water output retain sufficient total integrity, our attempts to restore a working balance will not appear clumsy. However, the difficulties of artificially achieving balance are increased as regulatory mechanisms become impaired. If the urinary function of the kidney is reduced too far, any therapy aimed at establishing balance becomes, in some way, the wrong therapy

1.3 *Water Intoxication* Many substances, if administered rapidly and steadily, accumulate in the body as toxic loads. Often the rate of growth of a load decelerates as excretion rate approaches intake rate but occasionally the kidneys become unable to cope with a rapidly developing load. They suffer a diminished ability to excrete, and load growth is accelerated Either of these conditions can be found when

12. *The Water Balance Statement in Man.* Table I provides an account of the water balance which might be found in an average man in some temperate environment, and the traffic borne by the various paths of intake and output. Its division of intakes and outputs into obligatory and facultative portions emphasizes the extensible nature of the water balance which can be attained at greatly different levels of water exchange. The *obligatory urine volume* is defined by Ambard and Papin[37] as that minimal volume of urine compatible with the excretion of the solid material contained therein. It forms daily even when fluids or food intake may be zero Its rate of formation is the *obligatory urine flow.* The *facultative urine volume* is any excess above the obligatory urine volume, determined by ingestion, and supposedly

TABLE I

A water balance statement for normal man (cc per 24 hours).

	Intakes		Outputs		
	Obligatory	Facultative	Obligatory	Facultative	
Drink	600	600	600	600	Urine
Water in food (preformed)	700	0	400	0	Skin
Oxidative water of food (potential, metabolic)	300	0	400	0	Lungs
			200	0	Feces
Subtotals	1600	600	1600	600	Subtotals
Total	2200		2200		Total

independent of physiological requirement In the balance statement we observe a 600 cc obligatory "drink" intake offset by the obligatory urine volume of 600 cc since the sum of the water contained in the normal food intake, plus the "potential" water of food which arises from its oxidation, offsets the obligatory outputs of skin, lungs, and feces.

Oxidative or "metabolic" water[12] is nearly proportional to the calorific value of food, 1000 Calories yielding about 100 to 140 grams of water. The total water requirement is roughly equal to 1 cc per Calorie During starvation almost no exogenous water is required by the body. Dogs, for example, ingest only one-quarter the usual amount of water upon interspersed days when no food is given[12, 602]

Richter[905] states that the average voluntary daily intake of water in rats, cats, dogs, monkeys, and man is 1142 cc. per square meter of

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1.3. *Water Intoxication* Many substances, if administered rapidly and steadily, accumulate in the body as toxic loads. Often the rate of growth of a load decelerates as excretion rate approaches intake rate but occasionally the kidneys become unable to cope with a rapidly developing load. They suffer a diminished ability to excrete, and load growth is accelerated. Either of these conditions can be found when

water is taken in rapidly and the syndrome of water intoxication may occur. Rowntree[916] has described this syndrome. In various mammals, it is characterized by restlessness, asthenia, polyuria, pollakiuria, occasional hematuria[410], diarrhea, salivation, frothing at the mouth, nausea, retching, vomiting, tremor, muscle twitches, ataxia, tonic and clonic convulsions, collapse, stupor, coma, and death in cardiac failure. There is hemodilution, including a decrease in serum crystalloids Oliguria is occasionally present The condition can be acute or subacute, lasting for days (§6 3) It can be prevented and usually cured by the administration of intravenous hypertonic sodium chloride or by oral administration of salt

According to Smyth, Deamer, and Phatak[1010] neither water retention in the body nor hemodilution are the most essential features of so-called water intoxication. They considered the convulsive symptoms to be more closely associated with loss of systemic chloride by way of the gastric secretion and the resulting alkalosis, noting that the loss of chloride by way of the kidneys is only about one-tenth the total loss while the greater loss is by way of vomitus In the absence of vomiting, as in the rabbit, the water in the stomach takes up chloride so the loss of this ion is effectively the same In this way chloride falls below its renal threshold in the plasma and is withheld from the urine, but its subthreshold concentration does not prevent its diversion from blood to stomach. Atropinized dogs do not develop symptoms of water intoxication so readily presumably because gastric loss of chloride is minimal Although these authors suggested that the effect of sodium chloride in relieving symptoms is so dramatic as to make it appear that chloride is more important than water in the syndrome, this is based on no quantitative evaluation of the relative importance of salt and water. "Heat cramps" or "miner's cramps"[20] present a picture similar to that of water intoxication. Since these are relieved by salt or saline they may constitute a type of water intoxication in which, instead of an absolute hydration or positive load of water in the body, there is a negative salt load. Further, urea diuresis, which is not highly chloruretic, is said to alleviate the symptoms of water intoxication. It is difficult to avoid the conclusion that both conditions are closely dependent on a lowered ratio of salt to water in extracellular fluids.

Several authors have described water *intoxication in human subjects.* Positive water balance with primary elevation of intake is seen in psychiatric polydipsia. The case is reported[63] of a dementia praecox patient who drank excessive quantities of water with resulting convulsions and coma, but with subsequent recovery. Death in convulsions has followed a cholecystectomy when 9 liters of water were absorbed

by proctoclysis within 30 hours[529]. Reduction of urinary water output together with elevation of water intake has also been studied McQuarrie and Peeler[759] have induced grand mal seizures readily in epileptic subjects under pituitary antidiuresis by excessive water loading. These effects are prevented by sodium chloride administration and are thus correlative with water intoxication

1.4 *Susceptibility and Resistance to Water Intoxication. Renal-Adrenal Relations.* Gaunt[409, 410] has shown that after adrenalectomy in rats, diminution in the ability to sustain a water diuresis occurs along with an increased susceptibility to water intoxication There is a delayed intestinal absorption of water as well as delayed excretion of absorbed water After large doses of water there is a lowering of plasma chloride and the hematocrit rises sharply, the latter probably reflecting an osmotic swelling of erythrocytes in their hypotonic medium The body temperature falls sharply, providing an excellent measure of the extent of water intoxication in normal and adrenalectomized animals.

Adrenal cortical extract and desoxycorticosterone acetate exert a protective action against water intoxication[352, 407]. Large doses of these in normal rats will prevent intoxication which would otherwise occur with large water intakes Whole cortical extract appears to be better in this regard than DCA, and compound E (17-hydroxy-11-dehydrocorticosterone) was found three times as effective as DCA. The amorphous fraction is only weakly effective when compared with whole extract of equal potency in maintaining life in the adrenalectomized dog

Resistance to water intoxication is also raised in rats by giving water orally in increasing but nontoxic doses for 5 days[660] Such resistance is not entirely dependent on the characteristically increased rate of diuresis (§8 7) since with vasopressin toxic symptoms are less at given water loads

1 5. *Water Deprivation* Just as renal activity can fail to prevent water intoxication, it can also be ineffective in neutralizing dehydrating influences McCance and Young[752] found that human subjects who had lost up to 7 per cent of their body weight in three or four days could, following large doses of sodium or potassium chloride in relatively small volumes of water (18 g./500 cc water and 12 g./100 cc. water, respectively), sustain a diuresis which led to a fall in the urine:plasma osmotic pressure ratio Thus, as water excess does not carry the insur-

ance of compensatory renal excretion, neither does water deficit necessarily bring restriction of urinary flow; and the composition of the urine is not necessarily conducive to the maintenance or restoration of normal plasma concentration. In fasting there is an initial diuresis and an increased negative water balance during water deprivation[1148]. On a standardized diet daily water output depends on salt intake, within limits, and is possibly regulated by factors other than plasma concentration.

1.6. *Equilibration.* Excesses or deficits of water, when carried to extremes, elicit renal responses which no longer follow the physiological pattern. When an excess of water becomes too great, diuresis may fall off[476, 1171]; and we may believe this to be some acknowledgement of overwhelming stress. When deficits of water become too great or salt excesses relatively too large, the kidneys, instead of further increasing urinary concentrations of minerals, may decrease them and at the same time increase water output[752, 886]. Both actions appear inconsistent with what might be supposed desirable and, indeed, there seems to be no theoretical justification for regarding either of these actions as favorable to the body economy. In a larger sense, however, the dipsogenic effect (§6.4, 7.12) here would be expected to favor the ingestion of water which in turn would tend to restore salt-water balances. It would not be surprising if such processes become explicable in some future science of "metaphysiology" whose subject matter deals with the laws of stress beyond the physiological.

In contrast to renal decompensations which are revealed only after sufficient provocation, the normal or physiological pattern is patently calculated to undo the effects of lesser provocation. There are well defined limits of excess or deficit within which renal and allied responses vary in some proportion to the stresses applied and undo or minimize strains. The equilibration diagram of Adolph[16] which evaluates the renal and extrarenal processes acting to re-establish and maintain water balance in man describes these nicely (Fig. 1).

Factors in Fluid Transfer

1.7. *Tonicity and Osmotic Pressure.* A red blood cell suspended in a salt solution of such concentration that no net flow of fluid crosses the cell membrane, that is, so that the cellular volume remains unchanged, is said to be in an isotonic solution.* This solution may or may not

* An *isotonic* (*isoplethechontic*) solution for rabbit erythrocyte is one containing 1.12 per cent sodium chloride[869].

be isosmotic with the solution within the cell. Isosmoticity is said to exist only if certain colligative properties of the solutions within and without the cell are the same. These properties, referable to the solvent, extend to freezing point depression, boiling point elevation, and lowering of vapor pressure.

At a time when physiologists set great store by the austere definitions of the physical chemists it is well to recall that the former have pre-

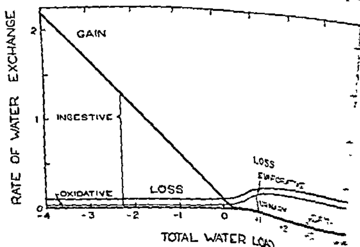


Fig 1 Equilibration Diagram for Man. Rate of water ... (... body weight/hr) in relation to water load (per ...

nearly independ...
Adolph [16].

empted the term "osmotic pressure" Bayliss ... us its meaning together with that of its cognate...

It is, perhaps, well to make a few remarks ... view held by some that osmotic pressure only ... of a semi-permeable membrane. If this is so, ... speaking of the osmotic pressure of a solution ... stances except those in which it is separated ... means of a membrane impermeable to solute ... that property of a solution which would ... pressure under these special circumstances ...

other method, such as freezing point, another name must be used

It is clear that such a practice, although perhaps in agreement with the original meaning of osmosis as used by Dutrochet, would give rise to much inconvenience, and even confusion We need a word to express the total concentration of a solution in such elements as act as molecules in the sense of Avogadro's law, since the molar concentration does not afford the information in the case of electrolytes and colloids. It seems to me that we are quite justified, even in theory, in speaking of the osmotic pressure of the blood, for example, without any reference, even in thought, to a semi-permeable membrane. We mean to express those properties conferred by the kinetic energy of the molecules, or elements equivalent to them, of the solutes In the presence of a semi-permeable membrane it would be shown as a definite pressure, capable of measurement by a manometer; but the phenomenon which causes this pressure is always there and leads to diffusion, amongst other things

This denying of the existence of osmotic pressure except in relation to a membrane leads to the denial of its existence altogether, since we know of no perfect semi-permeable membrane

No objection is made to the statement that the air in a vessel open to the atmosphere has a pressure of 760 mm of mercury, although it is not to be detected unless the vessel is closed and provided with a manometer while the outer atmosphere is removed

. . . I shall continue to use the words "osmotic pressure," meaning thereby that property of solutions conferred upon them by the kinetic energy of the solutes

The name *"tonicity"* is sometimes used, especially in reference to blood corpuscles and living cells in general, but it is not necessarily the same as osmotic pressure, unless we admit that the latter may vary according to the membrane used For example, we say that a solution of sodium chloride is "isotonic" with mammalian blood corpuscles, because it produces no change in their volume. But we might add an equivalent amount of urea to this solution without making it less "isotonic" with the blood corpuscles, because their membrane is permeable to urea On the other hand, its osmotic pressure is really doubled, as shown by vapour pressure measurements The word "isotonic" can only be used when the nature of the particular membrane is specified, and refers only to those constituents of the solution to which the membrane is impermeable; osmotic pressure refers to the total concentration, assuming that the membrane is impermeable to all the solutes, permeable to the solvent.

18. *Other Forces in Fluid Translocation.* Osmosis is not a necessary manifestation of either osmotic pressure or tonicity Physiologically, fluids do not flow across membranes merely in response to concentration gradients We may cite several complicating elements. There is the force which may be generated by the metabolic activity of the living cell This can effect a movement of fluids into and out of cells, and it is characteristic of such processes as secretion and absorption. Metabolic forces have direction and magnitude The secretory pressure of urinary fluid in the aglomerular tubules of the toadfish is in excess of that in the dorsal aorta[116]

Hydrostatic pressures, as evidenced in the circulatory system, in body cavities, and as intercellular fluid pressures, play a role which has been thoroughly evaluated in a few specific types of fluid translocation. The Starling hypothesis of capillary transudation[1022] and its clinical application by Epstein[346] to the volume imbalance known as edema has turned a physiological beacon upon a dark mystery

Electrical forces, manifest in membrane potentials, are thought to play a significant part in the regulation of fluid transfers across membranes. Nevertheless these and the secondary osmotic effects imposed by Donnan equilibria are not as yet indispensable to the formulation of qualitative working concepts of fluid transfer These forces are demonstrable but of uncertain consequence They are concerned perhaps more with local aberrations of concentration than of volume The Donnan equilibrium is not conditioned by the volumes of fluids separated by membranes, but only by their concentrations

Diffusion, in its simplest form, provides a means whereby fluid bulk can be moved about, within or between body compartments It is a factor in insensible pulmo-cutaneous perspiration and it is linked intimately to processes of osmosis In the excretion of substances like acetone and alcohol this process seems so characteristic that Ambard[36] was led to introduce the concept of "elimination by diffusion" on a par with elimination by "secretion" and by "effraction" Henderson[532], in criticizing the Fick theory of diffusion where the solvent plays an inert role, recalls a demonstration of Höber[546] in which "isotonic" solutions of magnesium sulfate and sodium chloride change in volume when brought in contact. The chloride diffuses faster than the sulfate and the sulfate solution becomes more concentrated. As a result water diffuses into it from the chloride solution Here, without outside work being applied to the system, a flow (anomalous osmosis) of both solute and water is caused to take place between "isotonic" solutions and an increase of several atmospheres of osmotic pressure may be induced in this manner, through differential rates of solute diffusion. The osmotic

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Diffusion, in its simplest form, provides a means whereby fluid bulk can be moved about, within or between body compartments It is a factor in insensible pulmo-cutaneous perspiration and it is linked intimately to processes of osmosis In the excretion of substances like acetone and alcohol this process seems so characteristic that Ambard[36] was led to introduce the concept of "elimination by diffusion" on a par with elimination by "secretion" and by "effraction " Henderson[532], in criticizing the Fick theory of diffusion where the solvent plays an inert role, recalls a demonstration of Hober[546] in which "isotonic" solutions of magnesium sulfate and sodium chloride change in volume when brought in contact. The chloride diffuses faster than the sulfate and the sulfate solution becomes more concentrated. As a result water diffuses into it from the chloride solution Here, without outside work being applied to the system, a flow (anomalous osmosis) of both solute and water is caused to take place between "isotonic" solutions and an increase of several atmospheres of osmotic pressure may be induced in this manner, through differential rates of solute diffusion The osmotic

other method, such as freezing point, another name must be used.

It is clear that such a practice, although perhaps in agreement with the original meaning of osmosis as used by Dutrochet, would give rise to much inconvenience, and even confusion. We need a word to express the total concentration of a solution in such elements as act as molecules in the sense of Avogadro's law, since the molar concentration does not afford the information in the case of electrolytes and colloids. It seems to me that we are quite justified, even in theory, in speaking of the osmotic pressure of the blood, for example, without any reference, even in thought, to a semi-permeable membrane. We mean to express those properties conferred by the kinetic energy of the molecules, or elements equivalent to them, of the solutes In the presence of a semi-permeable membrane it would be shown as a definite pressure, capable of measurement by a manometer; but the phenomenon which causes this pressure is always there and leads to diffusion, amongst other things.

This denying of the existence of osmotic pressure except in relation to a membrane leads to the denial of its existence altogether, since we know of no perfect semi-permeable membrane.

No objection is made to the statement that the air in a vessel open to the atmosphere has a pressure of 760 mm of mercury, although it is not to be detected unless the vessel is closed and provided with a manometer *while the outer atmosphere is removed*

. . I shall continue to use the words "osmotic pressure," meaning thereby that property of solutions conferred upon them by the kinetic energy of the solutes

The name "*tonicity*" is sometimes used, especially in reference to blood corpuscles and living cells in general, but it is not necessarily the same as osmotic pressure, unless we admit that the latter may vary according to the membrane used For example, we say that a solution of sodium chloride is "isotonic" with mammalian blood corpuscles, because it produces no change in their volume. But we might add an equivalent amount of urea to this solution without making it less "isotonic" with the blood corpuscles, because their membrane is permeable to urea On the other hand, its osmotic pressure is really doubled, as shown by vapour pressure measurements. The word "isotonic" can only be used when the nature of the particular membrane is specified, and refers only to those constituents of the solution to which the membrane is impermeable; osmotic pressure refers to the total concentration, assuming that the membrane is impermeable to all the solutes, permeable to the solvent.

1.8. *Other Forces in Fluid Translocation* Osmosis is not a necessary manifestation of either osmotic pressure or tonicity Physiologically, fluids do not flow across membranes merely in response to concentration gradients. We may cite several complicating elements There is the force which may be generated by the metabolic activity of the living cell This can effect a movement of fluids into and out of cells, and it is characteristic of such processes as secretion and absorption Metabolic forces have direction and magnitude The secretory pressure of urinary fluid in the aglomerular tubules of the toadfish is in excess of that in the dorsal aorta[116]

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tion to occur, the effective osmotic pressure of the plasma would increase with the loss of protein-free plasma filtrate (producing a rise in protein concentration in the plasma) until it again equaled the driving-out force Thus the processes tending to cause edema in this manner would be pulled up almost as soon as they started.

Although Starling[1025], Bolton[147, 148], Cohnheim[229], and others believed that increased permeability of the capillaries was necessary for the bulk transudation of fluid in cardiac edema, and although Smirk[994] has offered some evidence for this, even this additional factor is insufficient to account for the known properties of such edema.

Cardiac edema is poorly correlated with high venous pressure under crucial experimental and clinical conditions, and where correlation does exist, that fact alone cannot conclusively argue for causal relation. The work of Bolton[147, 148], Starling[1025], and Warren and Stead[1115] shows that edema often occurs where venous pressures are not elevated

1.11. *Hypoproteinemic Edema* The term "hypoproteinemic edema" describes little more than a correlation between the existence of hypoproteinemia and edema As with high venous pressure, the correlation between the plasma protein level and the presence of edema is poor[205] under crucial circumstances Edema may exist in the face of essentially normal plasma protein levels in malnutrition[292, 450, 600] and it may be produced by excessive intake of saline, accompanied by relatively little change in plasma protein level[1035].

For the same reason mentioned with regard to cardiac edema (that is, self-limitation of transudation) we should expect that where there is hypoproteinemia, an increased transudation on that account would result in a diminished plasma volume with a rise in plasma protein concentration until a new equilibrium was struck between forces of transudation and absorption But it is apparent that no large volume of edema fluid can be derived merely from the plasma volume.

1.12. *The Regulation of Compartmental Volume.* In terms of an equilibrium of osmotic and hydrostatic pressures, static or dynamic, across the collective capillary wall, there is nothing in the classical Starling hypothesis which accounts for or conditions the actual volumes of plasma and interstitial compartments So long as an equilibrium of this type only is assumed, the hypothesis defines no particular magnitudes for the volumes of the compartments involved As Hender-

son[532], McLean[757], and others have recognized, edema is essentially a perversion of volume regulation

1.13 *The Multicompartmental Nature of Fluid Exchanges in the Body* Perhaps the chief source of interpretive difficulty in the Starling hypothesis lies in the stylized treatment which has been accorded it, making it subserve a bicompartmental system of plasma and interstitial fluid, as if these were actually two discrete fluid bulks separated by a single collective capillary wall, and could properly be represented by the diagram in figure 2 In such a system fluid movements are simply

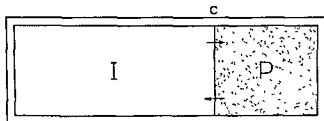


Fig 2. A Bi-Compartmental System with plasma *P*, interstitial fluid *I*, and collective capillary membrane *c* Net fluid exchanges occur only so long as appropriate pressure imbalances exist

the result of specific pressure imbalances in these compartments, osmotic, hydrostatic, or other, and a flow of fluid can continue only until these pressures again come into balance

Although he did not elaborate the idea, Starling recognized that the body is a multicompartmental system where an equilibrium is maintained not simply between plasma and some unit interstitium, but between plasma and a number of relatively isolated interstitial spaces, whose main connection with each other is through the plasma compartment There is probably no ready communication by *infiltration* between fluid in an interstitium of the arm and fluid in an interstitium of the leg, or between two relatively remote interstitia in a leg Any massive flow of fluid between two such otherwise isolated regions is accomplished through the plasma which behaves as a conductor. Application of the Starling hypothesis to a multicompartmental system readily removes the unsound aspects which prevail when it is considered on a bicompartmental basis.

1.14. *Fluid Flow in a Multicompartmental System.* How is it that a load of fluid taken into the plasma from an interstitial locus, *I*, is

compartments" at different fugacities Whereas at equilibrium all fugacities are equal and the hydrostatic and osmotic pressures of compartments *I, P, and J are balanced,* we can, *by properly altering the*

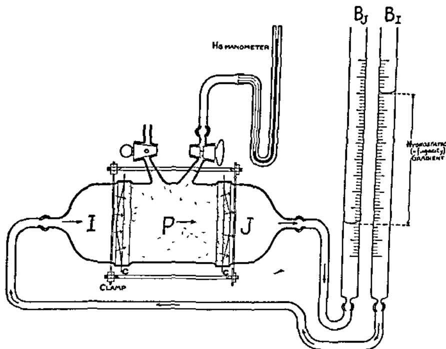


Fig 3. Osmometer–Transfer Cell (glass) "Plasma compartment" *P* filled with approximately 5 per cent gum acacia takes water from "interstitial compartments" *I* and *J* and reaches a hydrostatic pressure ca. 130 mm. of mercury at 27° C. Compartment *P* is separated from *I* and *J* by cellophane membranes *c* and *c'*. At equilibrium, levels in B_I and B_J are equal. Independently of the

concentration of the fluid contained therein. Even should the hydrostatic pressure and/or the acacia concentration change in *P*, the change occurs in the same way relative to *I* and *J* so that the gradient between B_I and B_J is not altered. The net rate of flow from *I* to *J* depends primarily upon the difference in their fugacities, and values for flow were obtained of the order of 8×10^{-4} cc/hr./mm. mercury pressure gradient/cm.² of double cellophane membrane

fugacity in one or both of the "interstitial compartments," effect a flow of fluid across "capillary walls" (*c, c'*). There need be no measurable change in hydrostatic pressure *in compartment P, no* change in the volume of that compartment, and no change in the osmotic pressure of the fluid contained therein In this manner a model multicompart-

mental system demonstrates how it is possible to effect a transfer across "capillary walls" with no more than the most minute changes in pres-

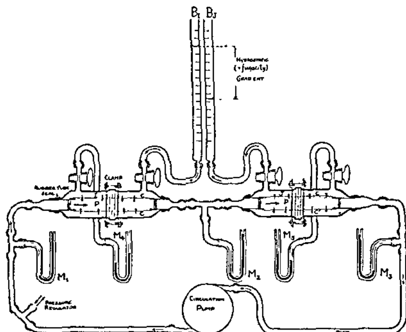


Fig 4. Osmometer–Transfer Cell with Circulation "Plasma compartment" *P* contains 5 per cent gum acacia, circulating "Interstitial compartments" *I* and *J* contain water which can travel from one to the other only by crossing cellophane membranes *c* and *c'* of the same type used in the osmometer–transfer cell of figure 3 M_1, M_2, M_3, M_4, and M_5 are mercury manometers With proper positive pressure at M_1 held constant by means of a pressure regulating device, fluid may be made to flow from *I* to *J* by maintaining a sufficient gradient of pressure between B_I and B_J, measured at M_4 and M_5, or, fluid will flow from *J* to *I* if pressure indicated at M_5 is greater than indicated at M_4. Even when there is no equilibrium so that fluid from B_I and B_J simultaneously enters or leaves *I* and *J*, the hydrostatic pressure gradient between B_I and B_J steadily diminishes Translocation of fluid from *I* to *J* or from *J* to *I* occurs quite freely even without a circulation, provided the pressure within the cellophane tubes is maintained steadily Rates of transfer between these compartments were of the same order of magnitude as for the osmometer–transfer cell in figure 3, namely, 1.6×10^{-4} cc./hr./mm. mercury pressure gradient/cm² of double cellophane membrane.

sures in the "plasma compartment" For every unit volume of fluid dV, entering compartment P, a unit volume, $-dV$, leaves simultaneously By means of the apparatus shown in figure 4 the same principle o

fluid transfer through a "plasma compartment" behaving as a conducto was shown to operate in a circulatory system.

A variant and more striking demonstration of the fugacity principle by mean of an osmometer transfer cell of the type depicted in figure 3 may be performe as follows. The central compartment, P, is filled with gum acacia starch solutio (95 cc. of 5 per cent acacia. 5 cc. of 1 per cent soluble starch); the other compart ments I and J are filled with a saturated aqueous solution of iodine. Initially th solution in P is substantially without color The manometer attached to thi chamber records the osmotic pressure of the solutes in it in terms of hydrostati pressure which stabilizes in a short time. During this period the solution in P becomes increasingly blue, in contrast to the solution in I and J, as the iodine *from these latter diffuses into P.* After the starch has become saturated with iodine it is possible, by keeping the hydrostatic pressure in I greater than in J (or vice versa), to maintain a steady state in which unlimited quantities of amber colored iodine solution can be passed into and through the blue solution in P; and the amber colored solution emerges from P, apparently unchanged despite thorough mixing with the blue fluid. The respective constancy of volume, pressure, and content of chamber P is indicated by the fact that the volume of fluid leaving buret B_I equals the volume entering B_J, by the fixed manometer reading for chamber P, and by the failure of the blue color to enter I or J. And the blue solution ("plasma") is seen in the role of a fluid conductor.

Kolff[610] cites dramatic evidence of the fugacity principle in connection with his studies of the "artificial kidney" (§4 19) "In the case of patients suffering from edema . we added more glucose (to the dialysing bath) namely 2 to 3% instead of 1 5% As it takes some time before all the glucose has dialysed in . an osmotic water movement *toward the bath water takes place* Indeed *we saw the patient's* edema shrink rapidly so that in some cases wrinkles appeared on the skin." Here the plasma is acting to conduct fluid from interstitial spaces to the bath water of lower fugacity. The plasma may be expected to suffer certain minimal changes in hydrostatic pressure, osmotic pressure, or volume, but *unlimited volumes of fluid may enter and leave the circulation* This observation of Kolff also argues effectively that rates of transfer across actual, physiological, fugacious gradients are great enough to account for known rates of accumulation of edema.

Finally, we may consider the operation of the fugacity principle in the removal of massive, generalized edema through Southey tubes or similar devices When a cannula is inserted into a subcutaneous, interstitial pocket of fluid at relatively high hydrostatic pressure, that pressure is promptly reduced locally with an expulsion of fluid. The fugacity *of the remaining fluid of that region* is thereby *lowered* with respect to the plasma and, consequently, with respect to the fluid in most other

interstitial compartments (§1.15). Even before fluid has been lost in quantities sufficient to diminish appreciably the venous pressure, the fugacious gradients erected between the fluid in the cannula and the excessive fluid in the thorax, abdomen, forearms, etc. conduce to a movement of fluid from these regions toward the cannula. Theoretically, the lowered venous pressure which may follow the removal of substantial amounts of extracellular fluid is not required for "mobilization" of the edema (although in particular instances it may aid it). If, as may be the case, the venous pressure were lowered with respect to that of the extracellular fluid in the region of the cannula in the same way as it might be lowered with respect to the fluid in remote edematous areas, the fugacious gradients among tissues and cannula would remain unchanged. As the generalized edema is conducted through the plasma and ultimately passed through the cannula, then, among other changes, the generalized tissue tensions decrease, the fugacity of fluid in these regions falls, and the fugacious gradients become too small to bring about appreciable, further drainage in this manner.

1.17. *Fugacity Equations.* For two interstitial compartments, I and J, and the plasma compartment, P, it may be stated that

$$F_I = F_P \qquad (2)$$

and

$$F_J = F_P \qquad (3)$$

where F is the fugacity of the compartmental fluid.* For simplicity we shall assume the plasma fluid fugacity at both compartmental sites is the same. Subtracting equation (3) from (2) we have

$$F_I - F_J = 0 \qquad (4)$$

On adding saline to compartment I, the new fugacity, F'_I, is

$$F'_I = F_P + f \qquad (5)$$

here f is the fugacity of F'_I in excess of F_P. Since equation (3) holds r the initial period following saline administration to compartment I, obtain by subtracting equation (3) from (5)

$$F'_I - F_J = f \qquad (6)$$

These equations do not deny the existence of exchanges of fluid at arteriolar venular ends of the capillary consequent to different pressure imbalances at sites. They do define (ignoring lymphatic drainage for purposes of simplification) a lack of any appreciable net exchange between entire capillaries and their late interstitial regions.

maintained sufficiently long is, of course, not simply a result of the increased hydrostatic pressure of the *blood* in those parts since the extravascular fluid undergoes corresponding changes in hydrostatic pressure with changes of body position.

1.19. *Fugacity and Tonicity* Fugacity is a physical concept having physiologically useful properties. It permits us to infer the direction of fluid movement and the partitioning of fluid bulk in the body when many critical data are lacking. Its application is not dependent on special knowledge of local conditions of hydrostatic, osmotic, tissue, and other pressures When we say a solution is isotonic for certain cells of the body we mean that, surrounded by it, the cells undergo no net transfer of fluid across their membranes Yet the hydrostatic pressure inside of a cell may conceivably exceed that of the ambient solution and without this pressure difference fluid would enter the cell Tonicity has no meaning without reference to a membrane of some sort between adjacent solutions (§1 7); and the nature of the membrane establishes the effectiveness of osmotic pressure across it in terms of its unique degrees of permeability for different substances Molecular species with differing diffusion coefficients and molecular volumes further contribute to the whole picture of what we call tonicity.

The concept of tonicity has not been formulated to include clearly the effect of hydrostatic pressure upon a solution or fluid Plasma at some pressure in capillaries is apparently "isotonic" with interstitial fluid while plasma (in capillaries) at the same hydrostatic pressure as interstitial fluid is apparently "hypertonic" To denote a given solution of plasma as isotonic and hypertonic, or even "hypotonic" (at elevated hydrostatic pressure in capillaries), does violence to the idea of tonicity as a fixed property of solutions with respect to given membranes A more comprehensive characterization of fluids in regard to their potential ability to cross membranes or liquid interfaces incorporates the effects of hydrostat[illegible]

is *hyperfugic* Plasma with respect to interstitial fluid and a capillary membrane is properly called hypertonic by virtue of the effective osmotic pressure of its richer protein content, but this implies the qualification that both fluids of the system be at the same hydrostatic pressure. "Isotonic" glucose is essentially isosmotic with "physiological saline," but it is not actually isotonic at least with reference to cellophane or

or, since $F'_I > F_J$, there is a tendency for fluid to flow from I to J, initially.

1 18 *Fugacities in Positive Water and Salt Balance* Starling[1023] clearly recognized that the intake of substances through the gut may continue although there may be a greater amount of them in the organism as a whole than it actually requires. He stated[1025], "The injurious results of any indiscriminate activity of the alimentary canal are counteracted by one of the chief organs which effect the output of fluid, viz, the kidneys" It is obvious that a large body of edema fluid accumulates only over a period of positive water and salt balance; and it is unnecessary to review here all the testimony favoring the view that an impaired renal excretion of these substances may exist[381, 392, 446, 1025, 1115]

We may state the fugacity equations which relate the alimentary intakes and renal outputs as follows Normally,

$$F_{gut}=F_P+f \tag{7}$$

$$F_P=F_{kidney}+f' \tag{8}$$

and, in water balance,

$$f=f' \tag{9}$$

By adding equations (7) and (8) we see that

$$F_{gut}=F_{kidney}+f+f' \tag{10}$$

These equations express the normal relations of fluid on the intake side (high fugacity with respect to plasma) to the fluid on the renal output side (low fugacity with respect to plasma) In processes associated with disease and edema formation, the factor f' may decrease appreciably, but the fugacity of the fluid from the gut remains greater than that of the plasma and therefore greater than that of many interstitial compartments (since $F_P=F_I$) * The fugacity of renal fluid marked for excretion, raised with respect to the plasma (synonymous with impaired renal function), has the effect that fluid taken in by the gut finds its way into extrarenal regions of lower fugacity, the exact distribution depending on the relative fugacities of all parts concerned, for example, fluid tends to collect in dependent parts, etc. The collection of fluid in the lower parts of the body when some given posture is

* Dicker[293] has shown, for example, that in edematous, hypoproteinemic rats water absorption from the gut is not less, but rather faster, than normal.

maintained sufficiently long is, of course, not simply a result of the increased hydrostatic pressure of the *blood* in those parts since the extravascular fluid undergoes corresponding changes in hydrostatic pressure with changes of body position.

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Widal[1138, 1139] believed that accumulations of edema fluid were volumes of water in the body bound to *retained chloride ions* Whether the chloride was increased in the body as a result of increased intakes of sodium chloride or of sodium bicarbonate (which was found to decrease the excretion of chloride), water would be found in excess corresponding to an osmotic or similar requirement imposed by the chloride load. Although this author denied the possibility of the *sodium ion playing a role, he provided a clinical hypothesis, satisfying* for several years, accounting for the hydropigenous effects of high intakes of sodium chloride or sodium bicarbonate

Blum[132, 133, 134, 135, 136, 137], apparently regarding the idea of retention of a primary ion as fundamentally sound, proceeded with a study of the diuretic actions of certain salts such as sodium bicarbonate *and* sodium *chloride and* compared *these with potassium* bicarbonate and potassium chloride He concluded that, if we must choose, the sodium rather than the chloride was of the first importance in the retention of edema water. Sodium chloride administration was shown to aggravate edema while potassium chloride and certain calcium salts did not Strangely enough this poorly conceived and tested *hypothesis of sodium predominance has left a persistent impression*, fortified by the observation that substances like sodium bromide[501] are edema-forming, which has colored much subsequent physiological thinking To bring out the specious nature of this hypothesis one has only to consider the effects of salts like sodium sulfate which have no edematigenous activity[1172, 1177] and which are able diuretically *to remove accumulations of edema*

2 3 *Ionic Combinations* The author[1173, 1177] has adopted the view, consistent with more experimental evidence, that there is no one ion which is, per se, identified with gross fluid retention The *retention* of water *relative to* electrolyte increments (loads) can be shown to depend in a definite way on the specific combination of anions and cations which must be loaded simultaneously. Thus, sodium bicarbonate and sodium citrate[652] are not so hydropigenous per unit load of sodium as is sodium chloride. Potassium chloride differs significantly from potassium bicarbonate, etc It is quite true that a higher correlation is observed between the accumulation of water and sodium than between water and any other ions, but correlation is not proof of causal relation, and a complex urinary physiology which has scarcely been opened appears to underlie this phenomenon. A fuller discussion of this will be deferred until Chapter VII.

2 4. *Distortion in Body Fluid Compartments* It has been held[993] that except as it participates in the regulation of their composition, the kidney is not actively concerned with regulation of the volume of body fluids Rather, such regulation has been thought to be governed by extrarenal factors. This point of view was never shared universally and has become less tenable, requiring revision[1123, 1124] as new research continues to implicate the kidney in volume regulation[302, 461, 532, 757, 881, 910, 952, 1115, 1170]. Peters[841] states a case for volume regulation when he remarks, "It may well be the fulness of the bloodstream which provokes the diuretic response on the part of the kidneys."

Henderson[532], perhaps most clearly, has set forth the concept of specific volume regulation as applied to the higher organism as a whole He stated, ". . . the regulation of volume has remained without any physico-chemical analysis . . . Contrary to a general though vague belief, the regulation of volume is theoretically independent of osmotic pressure regulation For example, if a kidney produces a liter of urine of the same freezing point as blood, it must have diminished the volume of the body and left the osmotic pressure sensibly unchanged . Statistically the volume of the urine must vary with the magnitude of the volume regulation, although in particular cases, it need bear no relation to this quantity"

McLean[757] in a similar vein considers edema as a problem in physiological regulation, and describes it as a perversion of the regulatory mechanism of volume Among others, Adolph[10, 11] has treated the general problems of body volume regulation at length, and Borst[154] has discussed some special problems (§7 14).

Recognition of processes for the regulation of body volume through excretion was urged by the author[1170] when it was noted that the rate of excretion of chloride, following intravenous injections of sodium chloride, was not simply dependent on the load of salt but varied directly with the concentration of the infusion fluid used as well. Having assumed that for a given load of chloride a greater distortion of the relative volumes of intracellular and extracellular compartments would occur with the more concentrated solution[1174], he drew a parallel between the increased distortion produced, and the increased rate of excretion of chloride per unit load of chloride. It was hypothesized that though the rate of salt excretion is otherwise proportional to its load, the kidney may be obligated to discharge loads not only as they are the greater, but also to maintain the bulks of fluid compartments in normal relations to each other Urea, which produces little distortion in body fluid compartments, shows no effect

urinary concentration of sodium and of chloride in such a way that, whereas the volume of the body is permitted to expand with the load of water, the concentration of the retained fluid is changed to one closely resembling plasma itself. Physiological saline is only "physiological" in the sense that some body cells like erythrocytes are content to survive in it for a time with no substantial volume changes So far as plasma (100 mEq chloride per liter or 0 6 per cent sodium chloride) is concerned, the chloride of an infused physiological saline (150 mEq chloride per liter or 0.9 per cent sodium chloride) is too concentrated, and only the formation of a urine still more concentrated in chloride will save the plasma from serious alteration respecting this ion Salt solutions of widely varying strength are actually equally "physiological" in that when they are loaded in the organism, appropriate renal responses prevent untoward deviations from normal body composition * Once the adjustments of concentration are effected by the kidney[1172, 1173], adjustments of volume become increasingly effective and the output of urine rises in the face of steady intake of saline until an equilibrium is finally established[1035]

2 5. *Pressure Imbalance and Volume Imbalance Edemas* Consider how, after extensive hemorrhage, the presence of interstitial reserves of fluid manifest themselves in hemodilution, and how, following plasmapheresis leading to marked hypoproteinemia, the formation of edema is facilitated These states reflect extreme fugacious imbalance Lesser degrees of these stresses might bring on imbalances not so readily detectable It is generally agreed that many fluid translocations are explicable simply in terms of gross alterations of pressure balances at some special site, or even generally at plasma-interstitium interfaces, or in terms of permeability changes in capillary walls These phenomena, regarded in proper perspective, are seen merely to evidence the operation of principles underlying a larger system concerned with the regulation of body volume Looking beyond the high correlation between extreme hypoproteinemia and edema, for example, we may see in the presence of edema fluid a factor which aids in maintaining plasma volume Without the retention of edema fluid, partitioned as it is between plasma and interstitia, plasma volume would shrink excessively if its protein level fell sharply[154, 1035, 1174].

* The term "physiological" which is used in this book frequently and with critical import, describes conditions consistent with the health of an organism or part thereof, and which may be maintained steadily for periods in which there is no worsening of that health

From what has been said here and in the previous chapter we may erect a general classification of edemas (Fig. 6) based upon two fundamental types, each independent of the other, and capable of existing together The *pressure imbalance* edemas are the special, often localized edemas which result from a primary imbalance between pressures exerted at the capillary wall. These include permeability alterations in the wall which change effective osmotic pressures Pressure edemas are *self-limited* in that they derive from capillary transudation, so that compensatory increases in opposing influences automatically set in. Thus, in venous congestion, an increased concentration of plasma protein

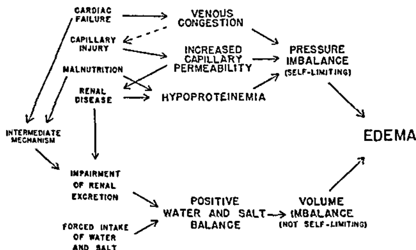


Fig 6 A Suggested Scheme Relating Factors Leading to Edema The nature of the "intermediate mechanism" appears at present to be conjectural (§ 2 5, 2 6, 7 14)

resulting from transudation opposes further transudation, and even where capillary permeability may be markedly increased as in shock, burns, etc , the total plasma volume available for transudation is limited.

The *volume imbalance* edemas are those which have no necessary dependence on any appreciable alterations in pressure balances but rather depend on alterations in the regulation of the volume of body compartments They often have their origin in a positive water and salt balance which may derive either from impaired renal excretion of water and salt or from forced intakes of these, or from both They are imbalances of volume in that the normal relations among sizes of body compartments are distorted, and they are *not self-limited* There

need be no measurable pressure imbalances across capillary walls although if such arise they do so secondarily to the creation of positive loads of water and salt The fact that these edemas may exist together, and largely independently, readily accounts for the further fact that we can often treat edemas successfully by attacking either of these roots, for example, cardiac or nephrotic edema can be reduced by removing fluid from the body (with diuretics) regardless of whether alterations of pressure balances (hydrostatic or osmotic) are specifically corrected.

2 6 *The Renal Factor in Generalized Edema. Enuresis and Ecuresis.* On a statistical basis some actual or relative impairment of renal function can be assumed to exist in order to account for the abnormal *accumulation of large quantities of fluid in the body.* *There is a renal* dysfunction of volume regulation[392, 532, 757, 1025, 1115, 1170] as well as dysfunction in concentrating power for sodium and chloride[392, 446]. It is known, for example, that in cardiac failure there is probably a lowered renal blood flow and reduced glomerular filtration[170, 773, 778], and the presence of a low venous pressure at times suggests that the reduced blood flow is not due to renal congestion and "backward failure."

Various investigators have suggested that some "antidiuretic factor" is involved in the production of edema Fremont-Smith[380] speculated about such a factor as a precipitating mechanism Robinson and Farr[910] found through rat bioassays on urine from patients with Bright's disease, premenstrual edema, Cushing's syndrome, and diabetes insipidus, that a correlation existed between the presence of clinical edema and the presence of an antidiuretic substance in concentrates of these urines. After recovery from edema the antidiuretic substance was no longer present. In patients given pitressin parenterally for seven days, the antidiuretic titer of the urine reached a maximum the first day and thereafter decreased rapidly to normal In three patients the urine became diuretic on the sixth day of continuous pitressin administration. The decrease in antidiuretic titer was paralleled by a *loss of edema caused initially by pitressin administration and these* authors thought that the body manufactured a physiological antagonist or otherwise destroyed the pitressin administered, including the normal circulating pituitary principle[524, 574]. Ralli, Robson, Clarke and Hoagland[881] and others[477] further encouraged the idea that an antidiuretic substance is involved in the formation of ascites. The finding of more of an antidiuretic substance in the urine of ascitics with

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Renal Physiology

Topophysiology; Clearance Concept

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Renal Topophysiology

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centration, but varies with protein intake[102]. A 3 per cent total protein concentration in urine is remarkably high, even pathologically, so that the concentration ratio, urine protein:plasma protein, is usually considerably less than 1. Inasmuch as the protein of smaller molecular weight (human serum albumin—mol wt, 72,000) tends to leave the plasma more readily than that of higher molecular weight (human serum globulin—mol wt, 150,000 to 190,000), albumin:globulin ratios for urinary protein tend to be greater than 1 and are found as high as 10 Conditions which favor proteinuria, therefore, tend to produce albumin globulin ratios for plasma protein which are less than 1.

Bull[195], in a comprehensive paper on so-called *postural proteinuria*, suggests the etiology of this condition as follows A rise in pressure in the inferior vena cava is produced by compression of the vessel against the spine by the posterior surface of the liver and this pressure is conducted back to the kidney inducing passive congestion and proteinuria The compression only occurs when the subject is in a lordotic posture and when the anterior surface of the liver rotates inferiorly This rotation of the liver normally occurs when the subject is lordotic and it is maximal in the erect lordotic posture. In some, if not all subjects, the site of compression of the inferior vena cava may be at the diaphragmatic opening and not below Accompanying proteinuria there is a fall in effective renal blood flow, a fall in glomerular filtration rate, and a rise in filtration fraction Proteinuria can be induced in subjects with large, easily palpable livers by rotating it inferiorly Delay in foot-to-tongue circulation time is associated with postural proteinuria

Some proteins, such as myohemoglobin or hemoglobin[666, 1187, 1188], are found to pass from the plasma to the urine more freely than plasma albumin or globulin Yuile[1186] elaborates the renal theory which considers the glomerulus effectively as a mechanical sieve containing innumerable pores each large enough to permit passage of certain large molecules It is assumed that there are pores of minimum and maximum size which set limits on the freedom with which different molecules may pass through. The upper limit is considered to be approximately at the level of the molecular size of hemoglobin (mol wt, 68,800) since under normal conditions no substances of higher molecular weight are known to pass through Clearance analysis suggests that only about 3 to 4 per cent of the pores are permeable to hemoglobin in the dog and 4 to 5 per cent in the rabbit. Myohemoglobin (mol. wt, 17,500) is excreted about 25 times more rapidly than hemoglobin and this is thought to be due to the more complete filtration of the smaller molecule.

Intraperitoneal injection of bovine albumin in rats has been found to

increase the excretion rate of intravenous hemoglobin for a given plasma concentration of hemoglobin, that is, it lowers the hemoglobin threshold[666] Possibly two factors are concerned in this phenomenon, namely, an increased glomerular permeability and a saturation of the transport system for protein reabsorption (§3 15–3 18)

Albumin is consistently present in the urine of infants in the second to fifth days of extrauterine life It is present even more markedly in the urine of premature infants[995]. Presumably some albumin normally filters at the glomerulus and is reabsorbed by the tubules in man as in other animals[303] Hemoglobinemia with hemoglobinuria is not always a benign phenomenon When marked, it is often associated with depressed renal function, tubular lesions, or nephrosis[122, 203, 636] However, there is evidence that hemoglobin can be prepared in a stable form and infused without evoking serious renal damage and that hemoglobinemia is probably not the basic factor in the production of renal lesions seen in certain clinical states[847].

The tubular reabsorption of electronegative colloidal particles such as hemoglobin, egg albumin, globulin, Trypan blue, etc is apparently different from that of crystalloids like glucose or urea Gérard[419] uses the term *athrocytosis* to indicate the intracellular flocculation which follows the absorption of such colloidal particles and their storage in the brush border segment of the tubules This process differs further from ordinary reabsorption in a prolonged retention of material in the tubular epithelium The earthworm with an open nephrostome in the coelomic cavity requires an athrocytic process to recover protein and other valuable dissolved materials which would otherwise be lost In the normal state the adult human kidney may never show marked athrocytosis, nor do most homoiotherms, but in disease, when colloidal particles pass more freely through the capsular walls, the athrocytic function, which has been lying dormant, appears In the dog the athrocytic capacity has been estimated at 2 mg/min for hemoglobin[790]

Increased lymph pressure in lumbar channels, leading to rupture of these vessels, is believed to play a role in the spilling of chyle *Chyluria* is evidenced by milky, cloudy, or white urine occasionally containing clots It is characterized by a colloidal suspension of fat particles which cannot be centrifuged, in contrast to *lipuria* in which fat in urine is in the form of globules visible to the eye and stainable with Sudan III Parasitic chyluria is a fairly common complication of filariasis, nonparasitic chyluria is of mostly unknown origin[686]. Chyluric urine may contain 1 per cent fat on a high fat diet and less than 0 1 per cent on a low fat diet Lipuria and albuminuria occur after decom-

pression of the briefly occluded renal artery of the dog. The fat may be secreted by the tubules[1099].

3.4 *Tubular Reabsorption, Passive and Active.* The tubular reabsorption of water, which in the mammalian kidney can produce a urine of greater osmotic pressure than the plasma, is regarded at least in part as an *active* reabsorption. Since such a urine in the tubules might be expected to oppose the reabsorption of water through its effective osmotic pressure, it is supposed that there is an expenditure of metabolic energy by the tubules, related to the difference in osmotic pressures between urine and plasma. "Osmotic work" may be performed on any substance (more properly, "by" any substance), including water, and this performance (or potential performance) is recognized by the existence of a difference of concentration between the plasma and the tubular or bladder urine for that substance This difference is known as a concentration gradient. Wherever there is a concentration gradient, there is a *concentration ratio* (urinary concentration·plasma concentration) greater or less than unity. Were "osmotic work" not involved in the creation or dissipation of a concentration gradient, then, aside from the effects of the Gibbs-Donnan equilibrium in heterogeneous systems, the concentration ratios should tend to unity, following free diffusion between urinary and plasma water

Acetone and alcohol are examples of substances whose free diffusion through the tubular walls probably accounts for the fact that their concentration ratios are always close to 1 despite tubular reabsorption of water which acts to create higher ratios[36, 1140] The type of reabsorption shown by acetone is assumed to be *passive*, conditioned by its minute concentration gradient between fluid of the tubular lumen and plasma, set up when water is withdrawn from the glomerular filtrate. There is reason to believe that urea is another substance showing passive reabsorption[721, 959, 961]. However, urea is thought not to be so freely diffusible through tubular walls as acetone or alcohol, and a greater concentration gradient between tubular fluid and plasma is set up during water reabsorption.

When a concentration ratio for any solute is different from 1, either it or water, or both, may be undergoing *active* reabsorption. If we admit the diffusibility of urea through the tubular wall in response to a concentration gradient, that is, its passive reabsorbability, then we can assume if we wish that any observed concentration gradient could have been set up by the abstraction of water from tubular fluid with

an expenditure of metabolic energy (for an alternate assumption, see §3.13)

A solute like sodium or chloride may at different times have a concentration ratio less than, equal to, or greater than 1. When it is equal to or greater than 1 we cannot decide whether reabsorption of solute is active or passive although some active reabsorption of water might be indicated where the ratio exceeds unity. A concentration ratio less than 1, however, implies in current thought an active reabsorption of the solute from the glomerular filtrate by tubular activity. The term "active reabsorption" applies to the process whereby a tubular transport system expends metabolic energy in moving a substance from the tubular fluid, across the tubular wall into the plasma It is called "active" by virtue of the belief that physical (osmotic) work must be involved, and it is called "reabsorption" because convention has given the name to that direction of transport

3 5 *Tubular Secretion* A transfer of substances in the reverse direction, that is, from the plasma to the tubular fluid, is called tubular secretion. It is consistent with the glomerular filtration theory that this process be always active for freely filterable, passively reabsorbed substances in the mammalian kidney A substance secreted by the tubules is usually deposited in a glomerular filtrate which already contains that substance in essentially the same concentration as the plasma water or in a higher concentration, as where some reabsorption of water from the filtrate has occurred This addition raises the concentration of the substance in the tubular fluid further. Thus, the concentration ratio for a substance secreted by the tubules is always greater than 1 although that fact alone does not prove that secretion is operating in any particular case *

In human renal excretion the greatest body of experimental and theoretical work tells us that water is normally filtered (120 cc /min) at the glomerulus in quantities considerably larger than the final volume of formed urine (1 cc /min.) and that tubular reabsorption (119 cc / min) of the greater bulk of the filtered water occurs. In aglomerular kidneys, as in the toadfish whose nephric units are merely blind tubules

* To the rule that the concentration ratio for secreted substances is always greater than 1 there are at least two exceptions. (1) A substance bound to plasma protein so that an appreciable fraction does not filter may at high urine flow be less concentrated in the urine than in plasma (but not in plasma water); (2) an actively reabsorbed substance, conceivably also secreted at some portion of the nephron above or below the site of reabsorption.

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3 7 When urea in solution is injected intravenously it diffuses to all parts of the body with great rapidity, the diffusion being almost complete in a few minutes Under many conditions its rate of excretion is directly proportional to its concentration in the blood[52, 721]. These facts taken alone imply that the rate of excretion of urea is proportional to its load in the body and that it obeys the law of exponential decay

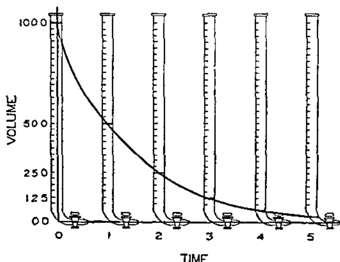


Fig 7 A Curve Illustrating the Law of Exponential Decay in the slow emptying of a buret whose outline and contained volume are indicated in the drawings superimposed on the curve at unit time intervals The buret, which contains 100 units of volume initially and which is set to empty in such a way as to contain one half that volume after one unit of time, will contain one quarter as much after two units of time, one-eighth as much after three units of time, etc

in much the same manner as radioactive disintegration, the electrical discharge of a condenser, or the slow emptying of a buret.

3 8 *The Law of Decay in Excretion* Consider the burets in figure 7. With a slow rate of emptying, the rate at any time, t, is proportional to the pressure head above the outlet and, therefore, to the volume, V. The equation describing the emptying of the buret is

$$V_t = V_0 e^{-kt} \qquad (11)$$

proximally, water finding its way into the urine must be secreted This particular kind of secretion was shown to be an active process by Bieter[116] who demonstrated that the pressure of urine delivered at the ureters of this fish can be greater than the dorsal aortic pressure The former pressure is of the order of 18 mm of mercury and the latter about 14 mm Since the main supply of this kidney is venous, the ureteral pressure is probably 4 or 5 times as high as the pressure in the renal capillaries

Marshall and Vickers[728] offered proof of the secretion of the substance phenolsulfonphthalein, known also as phenol red and PSP They showed that phenol red was largely adsorbed on plasma proteins so that only about one-fifth was free, diffusible, and filterable at the glomerulus (§3.15). Using estimates of the renal blood flow and the probable filtration rate in dogs, it was possible for them to show that more phenol red was found in the urine than could possibly have been contributed by the glomerular filtrate alone. The existence of the process of tubular secretion of phenol red was then posited to account for the excess of dye finally excreted Later, in answer to critics like Cushny[268] who would not incorporate the process of secretion into a theory of renal function, Marshall[719] showed that the dog kidney [illegible] in excreting phenol red than creatinine, which latter [illegible] the process of filtration alone (that [illegible] atively greater rate of excretion of phenol red than of creatinine (per respective unit plasma concentration) is considered sound evidence that a secretory process contributes to the final urinary excretion of the dye

3 6. *Ionic Exchange Summary* Pitts and his associates[864, 865, 866, 934] have proposed that there may be a "pseudosecretory" mechanism in which sodium ion is taken up by the tubular cells (Fig 10) from the luminal fluid in exchange for hydrogen ions given up to the luminal fluid Apparently a useful working hypothesis, pseudosecretion of hydrogen ion is believed capable of accounting, at least in part, for the process of acidification of the urine

In fine, the excretion of the constituents in urine is probably the result of a few fundamental processes: either filtration alone, where a substance entering the tubular lumen from the glomerular capsule passes into the final urine without undergoing any increment or decrement as a result of tubular transport, or filtration and active or passive reabsorption (or both), or filtration and secretion, or one or more of these processes, and "exchange."

where u is the rate of urine flow (cc./min.), U is the concentration of a substance (urea) in the urine (mg./cc.), and A is the concentration of that substance in the arterial blood plasma, essentially identical with the concentration in systemic, nonrenal venous plasma.* The value C, relatively constant at elevated urine flow, was called the "clearance" by these authors. The units of the clearance are given in cc./min. and the clearance itself is allied to a velocity constant of excretion. It is strictly defined by equation (13) as *the rate of excretion of a substance* (urea, in this case) *per minute per unit plasma concentration*. Another definition is almost equally valid. Transliterating the symbols of equation (12) we see that the urea clearance represents the number of cc. of plasma (flowing through the kidney in a minute), of a certain urea concentration, which would be required to supply the quantity of urea put out in the urine (the number of cc. of urine multiplied by the urinary concentration of urea) in one minute. Plasma flowing through the kidney is not, however, completely stripped of all its contained urea[1088], actually only about one-tenth of the urea is *removed from the renal arterial plasma, nine-tenths being left in the* renal venous plasma. The urea clearance, therefore, does not represent an actual quantity of plasma stripped completely of its contained urea during a minute's flow. It represents rather a *virtual* quantity of plasma, that is, a quantity which, *if* completely stripped of its urea, would provide the amount found in the urine formed in one minute.

If the renal plasma flow through the human kidney had been 750 cc./min. and the urea clearance 75 cc./min., then each of those 750 cc. of plasma flowing through the kidney might have been cleared of 10 per cent of its contained urea. But 75 cc. of plasma could have been stripped completely of its urea and provided the same quantity of urea for one minute's urine. Thus, it is proper to say that *the clearance of urea is the number of cc. of plasma virtually cleared of this substance in one minute*. This aspect of renal clearance is successfully employed empirically as a basis for renal function tests. When the urine flow is above its "augmentation limit" (§8.7), 75 cc./min. is a normal urea clearance in man. Clearance values appreciably below this are considered evidence of defective renal function, particularly glomerular.

Urea clearance is a unique function of the rate of urine flow. The exact relation has been the subject of numerous investigations[52, 222–224, 304, 306, 308, 478, 551, 959] and various empirical and semi-theoretical equations have been used to describe it, none completely

* For the significance of the error which may arise from the use of venous rather than arterial blood, see Brun, Hilden, and Raaschou[188].

where V_t is the amount of fluid left at the time t, V_i is the initial volume of fluid in the buret, e is the base of natural logarithms, and k is a "velocity constant." The curve of this equation, drawn in figure 7, has many interesting properties Its slope is always proportional to the height of the ordinate.* Equal time intervals are required for the buret to empty from its initial volume to one-half its volume; from one-half volume to one-quarter; from one-quarter to one-eighth; etc. Theoretically the buret would never cease to deliver fluid and would never empty were it not for the effective intervention of physical factors such as capillarity and evaporative loss, in the case of water. In the same way there are half-lives for radioactive elements which theoretically never disappear except for the fact that there are a finite number of atoms in a given mass and eventually the final particle disintegrates.

The *law of decay* is the opposite of the *law of growth* whose equation *has the same form as (11) except that the sign of the exponent of e* is positive. The multiplication of bacteria, the rate of increase in weight of young animals (the bigger they are, the more they eat, the faster they grow), and the increase of principal in the bank at compound interest (the compounding is performed every instant in nature) are *all instances of this cognate natural law.* Where the ordinate alone of the coordinates of a growth or a decay curve is plotted on a logarithmic scale, the curve is a straight line.

We could readily plot the rate of excretion of a load of urea against time and find an exponential curve similar to that of the emptying buret Many other substances such as inulin, acetone, and phenol red can show this same characteristic type of excretion.

39. *Clearance: The First Aspect.* Moller, McIntosh, and Van Slyke[787] studied further the excretion rate of urea and confirmed the proportionality of its excretion rate to blood or plasma concentration (and, therefore, to load). The relation could be stated that

$$uU = CA \tag{12}$$

or

$$C = \frac{uU}{A} \tag{13}$$

* The decay equation is derived from the premise that rate of emptying is proportional to volume, that is $dV/dt = -kV$, and equation (11) is the integral of this expression.

where u is the rate of urine flow (cc./min.), U is the concentration of a substance (urea) in the urine (mg./cc.), and A is the concentration of that substance in the arterial blood plasma, essentially identical with the concentration in systemic, nonrenal venous plasma.* The value C, relatively constant at elevated urine flow, was called the "clearance" by these authors. The units of the clearance are given in cc./min. and the clearance itself is allied to a velocity constant of excretion. It is strictly defined by equation (13) as *the rate of excretion of a substance* (urea, in this case) *per minute per unit plasma concentration*. Another definition is almost equally valid. Transliterating the symbols of equation (12) we see that the urea clearance represents the number of cc. of plasma (flowing through the kidney in a minute), of a certain urea concentration, which would be required to supply the quantity of urea put out in the urine (the number of cc. of urine multiplied by the urinary concentration of urea) in one minute. Plasma flowing through the kidney is not, however, completely stripped of all its contained urea [1088], actually only about one-tenth of the urea is removed from the renal arterial plasma, nine-tenths being left in the renal venous plasma. The urea clearance, therefore, does not represent an actual quantity of plasma stripped completely of its contained urea during a minute's flow. It represents rather a *virtual* quantity of plasma, that is, a quantity which, *if* completely stripped of its urea, would provide the amount found in the urine formed in one minute.

If the renal plasma flow through the human kidney had been 750 cc./min. and the urea clearance 75 cc./min., then each of those 750 cc. of plasma flowing through the kidney might have been cleared of 10 per cent of its contained urea. But 75 cc. of plasma could have been stripped completely of its urea and provided the same quantity of urea for one minute's urine. Thus, it is proper to say that *the clearance of urea is the number of cc. of plasma virtually cleared of this substance in one minute*. This aspect of renal clearance is successfully employed empirically as a basis for renal function tests. When the urine flow is above its "augmentation limit" (§8.7), 75 cc./min. is a normal urea clearance in man. Clearance values appreciably below this are considered evidence of defective renal function, particularly glomerular.

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* For the significance of the error which may arise from the use of venous rather than arterial blood, see Brun, Hilden, and Raaschou [1881].

In general, the clearance is greater as the rate of urine flow is greater. Austin, Stillman, and Van Slyke[52] found in man that urea clearance* rose with increase in urine flow until the latter reached a value between 1 and 2 cc/min. Above this value the clearance was not found to augment further and the term "augmentation limit" was applied to the critical urine flow In this sense the augmentation limit is probably a fiction There is actually no well-defined asymptote of "maximum clearance"[787] toward which urea clearances rise as urine flows increase. At present, renal theory would place the maximum possible urea clearance at the level of glomerular filtration This would be attained as the urine flow itself approached that level, but under conditions of such intense diuresis the glomerular filtration itself would probably increase

3.10 *The Second Aspect of Clearance.* Of more interest to renal physiology than the empirical use of the clearance as a renal function test is a second aspect of clearance which may be examined as follows.

Assuming that a given substance is neither synthesized nor decomposed by the kidney, neither stored in nor liberated from renal parenchyma, and not utilized,† then the quantity of that substance leaving per minute by both renal vein and urine equals the quantity arriving per minute via artery. We may state

$$aA = aR\ddagger + uU \qquad (14)$$

where a is the renal arterial blood or plasma flow to the kidney (cc/min.) and R is the concentration of the substance in renal venous blood or plasma in the same units as A and U (see Appendix).

$$a(A-R) = uU \qquad (15)$$

Dividing by A,

$$a\cdot\frac{A-R}{A} = \frac{uU}{A} = C \qquad (16)$$

Thus, the clearance of a substance is seen to be the product of the

* These authors did not use the term "clearance," which had not yet been introduced, but employed its mathematical equivalent.

† "Utilization" refers to the sum of the processes of metabolism and extrarenal excretion[307].

‡ The expression aR is used instead of rR (where r is the renal venous flow from the kidney per minute) at this point since a and r are almost equal The difference which results from using r instead of a is the one which is responsible for the fact that the two definitions of clearance previously given have different degrees of validity (§3.20). Lymph removal from the kidney is also neglected in this formula, being relatively insignificant in effect on the calculations to be made here.

blood or plasma flow, a, and the "extraction fraction," $(A-E)/A$ The extraction fraction, so named by Dunn, Kay, and Sheehan[313], is analogous in form to the "coefficient of utilization" for oxygen.

It is readily inferred from equation [16] that if a substance could be completely extracted from the arterial blood feeding the extracting or excretory portions of the kidneys (as opposed to the capsule, the ureters, and the perirenal fat), its extraction fraction would be 1 and its clearance would be numerically equal to the renal blood flow. Since it was shown histologically by Langley[643] that a not inconsiderable quantity of blood does bypass or shunt the renal artery and enter the renal vein via non-nephronic pathways, the clearance of the substance under discussion would not represent the total renal blood flow but rather the nonshunted flow. This latter is called the *effective renal blood flow*[1005] Substances probably handled by the kidney in this manner (diodrast, paraaminohippurate) will be examined later (§3 20)

3 11. *The Third Aspect of Clearance* The concentration ratio, U/A, is a fundamental renal variable It was first used by Gréhant[463] as an index of renal function Strictly, it is obtained by dividing the urinary concentration of a substance by its "average" plasma concentration prevailing during the formation of that urine The clearance is the product of the rate of urine flow and the concentration ratio

$$C = u \cdot \frac{U}{A} \qquad (17)$$

Smith[1002] has held that the two factors of the excretion rate, u and U must never be divorced, but it is precisely this factoring of excretio rate into two quantities which has proved informative in the study o interrelations in electrolyte excretion It is held here that the relatio between urine flow and concentration are susceptible of fruitful analy in the same way that the functional relations between heart rate a stroke volume provide information to the investigator of the he which would be obscured if attention were fixed merely on the prod of these variables, namely, the cardiac output

A list of concentration ratios is given in Table II The concentra ratio is a highly extensible physiological variable It varies inve with the urine flow for those substances which have constant clear For other substances such as urea, whose clearance increases wi rate of urine flow, the concentration ratio decreases with incre

urine flow but not along a rectangular hyperbola (Fig. 8). For still other substances, such as chloride, the concentration ratio is a complex

TABLE II

Urine plasma concentration ratios, U/A, found in normal man at two different rates of urine flow, $u = 1$ and $u = 2$ cc/min. The product of these concentration ratios and corresponding urine flows is the clearance. T and NT classify the substances as "threshold" and "no-threshold," respectively. Class T in this table includes, without distinction, thresholds of excretion and of retention (§ 7 2)

Substance	Class	U/A $u = 1$	U/A $u = 2$
Protein	T	<1	<1
Glucose	T	<1	<1
Amino acids	T	<1	
Water	T	1	1
Thiocyanate *		1	
Sodium	T	<1 to 2	<1 to 2
Chloride	T	<1 to 3	<1 to 3
Bromide	T	<1 to 3	<1 to 3
Bicarbonate	T		<1 to 3
Calcium	T	<1 to 4	
Magnesium *		5	
Phosphate	T	<1 to 16	
Sulfate	T		18
Uric acid	T	<1 to 24	
Potassium	T	<1 to 40	
Xylose *			50
Hydrogen ion	T	<1 to > 800	
Acetone	NT	1	1
Ethanol	NT	1	1
Urea	NT	54	38
Inulin	NT	120	60
"Exogenous" creatinine †	NT	175	88
Phenol red †	NT	400	200
Diodrast †	NT	700	350
p-Aminohippurate †	NT	700	350
Penicillin †	NT	700	350
Thiamin	NT	700	350

* Threshold nature not established.
† At low plasma concentration

function of urine flow and may either increase or decrease with it, or remain essentially unchanged.

If we first consider the concentration ratio of a substance like phenol red and recognize that this substance is excreted in part by the process

of tubular secretion, and then consider the concentration ratio for urea, and recognize that due to its highly diffusible and penetrating nature it is probably reabsorbed by the tubules to some extent, it becomes intriguing to speculate that there may be a concentration ratio between these two which belongs to some substance neither secreted nor

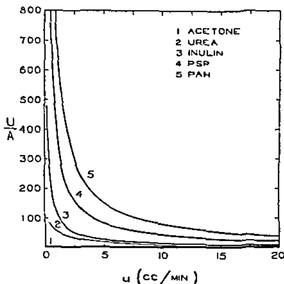


Fig 8. Relation of Urine Plasma Concentration Ratios (U/A) to Urine Flow (u) in Man. Curve 1 is given as a straight line. Curve 2 belongs to no well defined family of curves and the values of U/A when u is very small may or may not be constant [743] The product of the coordinates at any point of any curve is equal to the plasma clearance of the substance indicated Curves 3, 4, and 5 are given here as rectangular hyperbolas although the clearances of the represented substances are not always totally independent of urine flow

reabsorbed The properties of such a substance are extremely interesting If the glomerular filtration rate, g (cc /min), is multiplied by the concentration of this substance in the plasma, the product, representing the quantity of this substance filtered per minute, is equal to the quantity excreted in the urine per minute This follows because the tubules neither add to, nor subtract from, the filtered quantity in its passage to the bladder, that is,

$$gA=uU \tag{18}$$

and

$$g=\frac{uU}{A}=C \tag{19}$$

uU_x/A_x should be independent of the plasma concentration. Th condition in large measure excludes the possibility of tubular excreti and tubular reabsorption. *(3b)* Where *(3a)* cannot be demonstrat

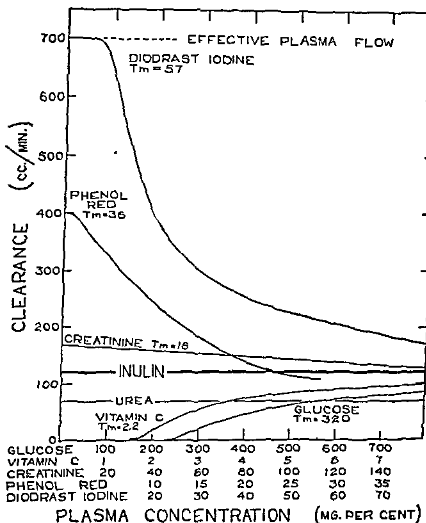


Fig. 9. Diagrammatic Summary of Excretion of Various Types of Compounds by the Human Kidney Modified from Smith [1002].

because of inconstancy in the rate of filtration itself, it is of equal force to show that the clearance of x is constant, relative to the clearance of some other substance, at various plasma levels of x. *(4)* Assuming that adequate doses of phlorizin completely block the tubular

reabsorption of glucose, then in the phlorizinized animal the clearance of x would be equal to the glucose clearance (This, of course, is not evidence that phlorizin does not block the tubular reabsorption of x itself.) *(5)* Where the simultaneous clearances of two or more substances are identical under a wide variety of conditions (plasma level, urine flow, etc), this may be taken as evidence that both substances are excreted by the glomeruli, without interference from the variable factors of tubular reabsorption or tubular secretion *(6)* Where a completely filterable substance is excreted in part by tubular activity, the clearance of that substance when depressed by elevating the plasma level should approach the clearance of x as the limiting asymptote

Of each of these points it may be remarked correspondingly· *(1)* This is a necessary but insufficient condition to establish a particular substance in the role of a standard *(2)* This is neither direct nor indirect evidence Presumptive or circumstantial evidence cannot constitute proof. *(3a)* This is a necessary but insufficient condition to establish a particular substance in the role of a standard Urea, acetone, inulin, and other substances fulfill this condition and have widely different clearances *(3b)* This is presumptive evidence Urea and acetone have clearances which can be constant relative to the clearance of inulin and certain other substances *(4)* This is a resort to a subsidiary hypothesis whose validity has not been completely established Indeed, Conway, Fitzgerald, and MacDougald[238] not only deny that phlorizin blocks the tubular reabsorption of glucose but also indicate that glucose may actually be secreted into the lumen of the proximal tubule in the frog. This is said to occur with no water reabsorption in this tubular segment, directly contradicting the observations of Walker et al [1106] which are alleged to have been misinterpreted Furthermore, as Smith has indicated, we do not know that phlorizin does not alter the tubular handling of x itself. *(5)* This is presumptive evidence Actual experimental error makes it difficult to distinguish small differences in clearances accurately, with the result that substances of different nature may only appear to be handled similarly Also, the nature of this evidence does not exclude the possibility that many substances remain to be investigated which may behave as members of groups in such a way that groups differ from each other by having different, characteristic, mean clearances, while members of a group have closely similar or identical clearances *(6)* This is possibly the best, if indirect, evidence. However, it is based on an assumption that the clearance of x is at the level of a clearly defined asymptote. Actually, several substances with appreciably different clearances have been used asymptotically, for example, xylose, when it was believed to measure glomerular

clearance,* and later inulin Clearances have found themselves approacl ing the asymptote theoretically most attractive at a given period i renal physiology

The above criticisms directed at the use of *test standards to measur* glomerular filtration are not intended to negate the value of attemptin; to exploit such substances but rather to point up the hazards whicl are run as long as clear criteria of equivalence between clearance an glomerular filtration rate are lacking for all conditions under whicl these standards are to be used. When it is argued[1000] that it i implausible for substances of such different natures as inulin, creatinine and thiosulfate to be either excreted or reabsorbed by the tubules t precisely the same extent in different species of animals, and that i may be accepted that in these species the substances are excreted by filtration without tubular participation, we should seriously question the evidential nature of implausibility. What assurance can be given that the inulin standard remains inviolate when it can be said that in the dog, its clearance is numerically equal to that of creatinine and thiosulfate, yet in man its clearance is lower than that of creatinine, and in the cat[120] its clearance is lower than that of thiosulfate? It is well to know the limitations of such a standard if it is used to judge the behavior of other substances in renal excretion Eggleton et al.[323] caution, "As disillusion has so often followed the most convincing advocacy of renal theories, it may be well . . to summarize . . . results which can easily be expressed in a form independent of theoretical beliefs, even the belief that the creatinine clearance is related to the rate of glomerular filtration."

A number of Smith's views on renal function, but particularly those concerned with the measurement of glomerular filtration, have been attacked root and branch by Ekehorn[*329–331, 333*]. *The latter* author prefers to retain the use of creatinine as a standard substance, after Rehberg[890, 891], while Smith[1002] asserts that the use of creatinine is erroneous Whichever position has the greater validity, it is *apparent that exhaustive analysis of this question has failed* to produce an answer satisfying to all investigators. Conceivably, any contention of this nature may be unverifiable

Failure to re-examine first principles can generate suspicious consistency in experimental effort When the clearance of a standard substance falls, as in disease, can we be certain that the glomerular filtration rate has decreased and that tubular reabsorption has not

* The *glomerular clearance* of any substance, freely filterable, is theoretically equal to the glomerular filtration rate, that is, $g = C = uU/A$, where U/A for capsular "urine" is 1, and $u = g$

occurred? How can we credit the reliability of the inulin-measured filtration rate in disease if inulin does not measure satisfactorily the filtration rate in the isolated kidney[969]? When it is found that in the rabbit[579] the clearance of inulin decreases with decreased urine flow and shows a precipitous drop as urine flows fall below 1 cc./sq m./min., how can we be certain that glomerular filtration is changing in direct equivalence to the inulin clearance and that tubular reabsorption of inulin remains at zero? And if protein is admittedly reabsorbed by the tubules[303] how can we exclude inulin (mol. wt., 5100) or mannitol (mol. wt., 182) from possible reabsorption?

McCance and Widdowson[748], in a case of alkalosis, and Keith King, and Osterberg[586], observing dehydration following large doses of potassium, found that the clearance of potassium could be greater than that of inulin. They accepted the implication that potassium, ordinarily reabsorbed, could also be secreted. This remarkable proceeding apparently signifies that potassium has properties common to both threshold and no-threshold substances (§3.16). Berliner and Kennedy[103] and Mudge, Foulks, and Gilman[795] support the hypothesis that potassium can be secreted as well as reabsorbed. They do not believe that the filtration rate in their experiments could have exceeded the clearances of creatinine, inulin, and thiosulfate, which are equal in the dog[434].

Barclay et al.[67, 69, 71] conceive a definite three-component system of renal excretion for a variety of substances including potassium, phosphate, urea, and members of the sulfonamide group. They hold that these substances may undergo one, two, or all three of the processes, namely, filtration, reabsorption, and secretion, in the course of being transferred from plasma to bladder urine. The evidence for the operation of these processes is based on the form of the curve obtained when the index E is plotted against A_s. This index is defined as

$$E=\frac{(U/A)_s-1}{(U/A)_{in}-1} \quad (20)$$

For many substances, and particularly at low urine flows, E can be approximated by the ratios C_s/C_{in} or by $uU_s/C_{in}A_s$, that is, the amount of solute excreted per minute divided by the amount filtered per minute. Providing a method of analysis, the index E is of considerable interest although one may doubt that the conclusions drawn from such analysis constitute the "only possible explanation of the excretory behavior of the kidney" even in selected cases.

Let us for the purpose of argument consider an unorthodox "secretion-filtration-reabsorption" theory (to be called here a "secretion"

theory) which holds that of the substances making up the urine, not including water, the larger part is secreted by the tubule cells while only some small quantity of water and crystalloids is added by the glomeruli. Some water may be secreted by the tubules but this is not essential to the theory. Further, let it be held that small, filtered quantities of glucose and some other substances are normally reabsorbed or utilized by the tubules and therefore do not appear in the urine Such a view resembles in important particulars that of Heidenhain[507] and some others For the moment let us consider points in favor of, or at least consistent with, such a theory, disallowing the tenet that inulin clearance measures glomerular filtration

Secretion does not require a uniquely high rate of capillary transudation The rate of glomerular filtration could be in accord with those of renal lymph flows (<1 4 cc /min) No astonishingly high rates (120 cc /min) need be contemplated Hemodynamics previously based on the assumed fact of the higher filtration rate could probably, without violence to underlying hypotheses, be based on a lower rate on equally rational terms. Renal arterial–venous–glomerular–ureteral pressure relations provide no direct contradiction to a secretion theory. They are at present no more than compatible with current theory and do not prove it

Secretion of water is a tenable physiological principle. Water can be secreted by the tubules of aglomerular fish It is not less reasonable to suppose that water can be secreted by similar cells in mammals than to suppose, as has been done, that because inulin is not secreted by aglomerular kidneys it is, therefore, not secreted by mammalian tubules Tubular poisons such as cyanide often produce an oliguresis, or at least no remarkable diuresis[466, 678, 1026]. This is consistent with poisoning of a tubular secretory mechanism for water rather than a tubular reabsorptive mechanism, allowing that the main contribution of water is from the glomeruli. Changes in the latter could account for such observations as the increase of urinary flow in certain phases of mercury poisoning Depressed urinary excretion of solutes is readily accounted for by assuming that their secretory transport mechanisms have been attacked by the poison

Concentration ratios U/A values greater than 1 for solutes are not more evidence for reabsorption of water by tubule cells than they are for secretion of solutes by these cells.

Secretion and the law of exponential decay. The fact that the excretion rate of inulin or that of many other substances, for example, acetone, urea, or phenol red at low plasma concentrations, is proportional to

plasma concentration does not prove that these are excreted only by filtration. Investigators have had no qualms about maintaining, for example, that urea can be passively reabsorbed[999], actively reabsorbed[998], or secreted[1107]. A constant clearance even over a large range of plasma concentrations may simply evidence the operation of the ubiquitous law of exponential decay (§3 8) in any one or more of many different possible systems Consider for a moment (in the current theory of *Tm;* §3 15–3 18) the tubular reabsorption of glucose when it is below its threshold of excretion The quantity reabsorbed is proportional to the quantity present in the tubules Turn this argument to phenol red below that plasma concentration at which self-depression of phenol red clearance begins Not filtered freely, it is nevertheless said to be secreted at a rate proportional to its quantity in the blood since its clearance is constant; the filtered contribution is likewise proportional to the quantity in the blood The self-depression and self-augmentation of certain clearances (Fig 9), with their approach toward the clearance of inulin as their plasma levels rise, has been a potent argument favoring the hypothesis that inulin clearance equates to glomerular filtration rate We have questioned this earlier In answer to the charge that many unlikely assumptions must be made if we are to discard current theory for some other such as the one under discussion, we note that the apparent unlikeliness of such assumptions merely reflects the degree of our ignorance in the whole matter Mass action and competitive reabsorption–secretion (§3.17, 3 18, 3 19) are probably as consonant with the secretion theory as with current theory

The augmentation phenomenon "Washing out" effects on certain solutes during diuresis could represent merely a general secretory stimulation induced by whatever diuretic agent is concerned Curves for many substances, for example, acetone, urea, inulin, and creatinine, relating clearance to urine flow, show that in some range the two variables increase together. Where inulin is not granted singular properties, the differences in these curves[224, 579, 959, 1146] fit into the secretion theory in terms of specific differences in handling of these substances by the tubules

Secretion of electrolytes Certain electrolytes, for example, potassium, are currently believed capable of being both secreted and reabsorbed by mammalian tubules Such handling, changed as conditions differ, could reflect little more than differing relative secretion rates where filtration is minimal, as in the secretion theory we have arbitrarily proposed

theory) which holds that of the substances making up the urine, not including water, the larger part is secreted by the tubule cells while only some small quantity of water and crystalloids is added by the glomeruli. Some water may be secreted by the tubules but this is not essential to the theory. Further, let it be held that small, filtered quantities of glucose and some other substances are normally reabsorbed or utilized by the tubules and therefore do not appear in the urine. Such a view resembles in important particulars that of Heidenhain [507] and some others For the moment let us consider points in favor of, or at least consistent with, such a theory, disallowing the tenet that inulin clearance measures glomerular filtration

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tion put here is whether we now possess a body of proper, scientific evidence for that view or whether some alternate concept could not be made out, substantially as logical and ultimately as useful.

3 14. *Glomerular Intermittence.* The question of whether the glomerular circulation is constant or undergoes some physiological type of intermittent activity has attracted a rather steady interest In large measure its answer determines the kind of working hypotheses renal physiology shall employ.

Richards and Schmidt[901] made direct observations of the glomerular circulation of the frog and reported intermittence of activity. For several years following, little progress was made in extending these observations either in the frog or in the mammal, but they were responsible for a growing common belief in the general occurrence of intermittence Adolph[13] repeated these studies, incorporating certain experimental procedures such as the induction of anoxia In the absence of oxygen urine formation ceased (only 4 per cent of an atmosphere of oxygen was required to prevent this reaction) with the flow in all glomeruli stopped by a constriction of arterioles rather than by any general circulatory effect Denervation had no influence The effects of anoxia, therefore, were similar to ligation of the renal arterioles Whereas Richards and Schmidt had surmised that flow through the glomerulus was a function of the call for oxygen and that glomerular flow would be a response to lack of oxygen, this was not the case Adolph conjectured that intermittency in the sense of a temporary cessation of circulation from groups of glomeruli was actually uncommon and was best seen only in animals whose circulations had suffered interference. However, Ekehorn[332] inferred from direct observation that only about one-tenth of the glomerular capillaries *per unit glomerulus* were open to the bloodstream at once, indicating that intermittence of an intraglomerular nature might occur Hyperemic glomeruli, utilizing the "functional reserve" of the glomerular capillaries, can be produced upon appropriate stimulation

Glomerular intermittence, in the sense of interglomerular alternation of activity, was investigated by White[1126] in normal dogs and rabbits Experiments of short duration during which India ink was injected into the renal artery, followed by histological examination, led him to the conclusion that the mammalian kidney showed all of its glomeruli open all of the time, that is, that there was no intermittence, at least under such conditions. No visual evidence for glomerular intermittence was found by Walker and Oliver[1108] either

Thresholds. Thresholds of excretion and retention (§7.2) ca accounted for under the conditions postulated by the secretion t as well as under those of our currently acceptable system.

Comparative anatomy; human pathology. Comparative ana suggests that secretion is a primitive function of the kidney; Oliver[observes that ". . whatever the uncertainty of physiological evid as to what constitutes tubular activity in the normal kidney, th the aglomerular nephron (in man) must consist of something than absorptive processes that act on a glomerular filtrate."

The arguments in favor of a secretion theory, like most of which have been used to support current theory, prove little. are presented simply to suggest that it is possible to establish parable degrees of credibility for the one theory as for the o Perhaps they exemplify the futility of reasoning out a theory of r function. How many will accept today the ratiocination of Brodie[when he tells us the glomerulus is a secreting and not a filtering surf

Despite protest to the contrary, nothing in a secretion theory cludes our learning empirically and theoretically the laws which operate in such a system There is no sound reason to suppose "secretion" will be any more refractory to experimental analysis t "reabsorption" Neither Cushny's dialectical attack on the secre theory[268], nor its more modern variants[999], give assurance it will not turn out eventually to be fundamentally sound. I needlessly hypercritical to belabor, but germane to observe with further comment, the inadequacy of Cushny's defense of his filtration-reabsorption theory in view of the contrariety of experime findings[728] then current.

Many statements, to accord with a secretion theory of renal ex tion rather than with current theory, need only verbal reorientat somewhat after the manner of Poncelet's Principle of Duality* wher the terms *secretion* and *reabsorption* are interchanged appropriat There is at present no evidence, independent of inulin clearance analy which militates decisively against such substitution. The relucta of the author to adopt without reservation the canon of the inu clearance is based neither on a disbelief in the absolute validity the method nor on a wish to espouse some more cherished doctri Perhaps the former will some day be established unequivocally to t vast satisfaction of all renal physiologists. The substance of the qu

* All the propositions of plane projective geometry occur in such pairs that fr either proposition of a particular pair, the other can be inferred by interchang the words *point* and *line* Thus, two *points* are on one, and only one, *line*; two *lin* ... and only one, *point*, etc.

tion put here is whether we now possess a body of proper, scientific evidence for that view or whether some alternate concept could not be made out, substantially as logical and ultimately as useful.

3 14 *Glomerular Intermittence.* The question of whether the glomerular circulation is constant or undergoes some physiological type of intermittent activity has attracted a rather steady interest. In large measure its answer determines the kind of working hypotheses renal physiology shall employ.

Richards and Schmidt[901] made direct observations of the glomerular circulation of the frog and reported intermittence of activity. For several years following, little progress was made in extending these observations either in the frog or in the mammal, but they were responsible for a growing common belief in the general occurrence of intermittence Adolph[13] repeated these studies, incorporating certain experimental procedures such as the induction of anoxia In the absence of oxygen urine formation ceased (only 4 per cent of an atmosphere of oxygen was required to prevent this reaction) with the flow in all glomeruli stopped by a constriction of arterioles rather than by any general circulatory effect Denervation had no influence The effects of anoxia, therefore, were similar to ligation of the renal arterioles Whereas Richards and Schmidt had surmised that flow through the glomerulus was a function of the call for oxygen and that glomerular flow would be a response to lack of oxygen, this was not the case Adolph conjectured that intermittency in the sense of a temporary cessation of circulation from groups of glomeruli was actually uncommon and was best seen only in animals whose circulations had suffered interference. However, Ekehorn[332] inferred from direct observation that only about one-tenth of the glomerular capillaries *per unit glomerulus* were open to the bloodstream at once, indicating that intermittence of an intraglomerular nature might occur Hyperemic glomeruli, utilizing the "functional reserve" of the glomerular capillaries, can be produced upon appropriate stimulation.

Glomerular intermittence, in the sense of interglomerular alternation of activity, was investigated by White[1126] in normal dogs and rabbits Experiments of short duration during which India ink was injected into the renal artery, followed by histological examination, led him to the conclusion that the mammalian kidney showed all of its glomeruli open all of the time, that is, that there was no intermittence, at least under such conditions. No visual evidence for glomerular intermittence was found by Walker and Oliver[1108] either

in anesthetized guinea pigs or rats, or in some other mammals. Their observations revealed that after oil droplets had been injected into the tubules the oil column formed therein showed at its proximal end the effect of pulsatile movements apparently transmitted to it from the glomerulus. These continued without interruption, constituting evidence for a lack of intermittence of glomerular activity in these preparations. Shannon et al [966] and Smith[1002] have supported this view of the mammalian kidney by their analyses of clearance data. However, Handley et al.[483] find evidence in clearance analysis *that dehydration may decrease, and hydration increase, the number* of active nephrons in the dog

Trueta et al [1072, 1073] have reopened the problem of glomerular intermittence in the mammal (rabbit) as a result of extensive studies based on direct observation of the renal circulation by means of a variety of specially developed techniques including angiography. They conclude

> The course taken by the blood in its passage through the kidney does not show that degree of constancy which has commonly been imagined. In fact, the kidney has two potential circulations, a *greater and a lesser, and in extreme conditions the blood may pass* either almost exclusively through one or other of two pathways, or, in less abnormal circumstances, to a varying degree through both The vessels making up the pathway of the greater circulation are those associated with the cortical glomeruli; the channels of the lesser circulation are those associated with the juxtamedullary glomeruli. . . .
>
> The blood reaching the kidney has two potential routes through that organ . The two routes diverge where the afferent arterioles of the juxtamedullary glomeruli leave the interlobular arteries. One route, the medullary, continues through the juxtamedullary glomeruli, the efferent vessels of the glomeruli and their derivative vasa recta, to the interlobular veins The other route, the cortical, continues through the interlobular arteries, the afferent arterioles of the remaining glomeruli, these glomeruli themselves, their efferent vessels and the cortical intertubular capillary network into which these break up, and finally through the veins draining this network into the interlobular veins. The rest of both routes, like their beginning, is identical and is through ever larger venous trunks to the main renal vein

The effects of these latter studies remain to be elucidated Thi concept of a renal circulation subject to the grossest kind of inter mittence as a result of nervous, humoral, or chemical activity (§9.11,

is fraught with possibilities for the reinterpretation of experimental results, but thus far it is not clear that such marked renal circulatory effects can be obtained in other mammals[894, 1086] or that they have functional significance In the rat, the renal vein may be occluded for 30 minutes (60 minutes in the dog) without appreciable pathologic or functional change, whereas the whole kidney pedicle can be occluded for more than twice this period without serious damage (§8 6) The characteristic lesion of occlusion of any type reflects degeneration of the epithelium of the proximal tubule The distal tubule and glomeruli remain relatively unaffected except in more prolonged occlusion Scheibe et al [931] discuss the variance of these findings with the implications that Trueta shunts may bring about lower nephron nephrosis (in which the distal tubule is affected selectively) through cortical ischemia.

Simkin, Bergman, Silver, and Prinzmetal[986] have proved that arteriovenous anastomoses, considerably larger than capillaries, exist in man and are normally patent in rabbits and dogs This was ascertained by injecting tiny glass spheres of known size into renal arteries and checking the sizes of the spheres recoverable in renal venous blood Spheres up to 180 micra in diameter were recovered in living animals and spheres up to 440 micra from postmortem kidneys of man It would seem that such passages are capable of conducting large quantities of blood and presumably have physiologic significance. They are thought by Black and Saunders[126] to account for the occasional fall in inulin and paraaminohippurate clearance found in cats and rabbits when the sciatic nerve is stimulated

3 15 *Tubular Reabsorption and Secretion* Normally, little glucose is found in bladder urine but it is filtered from the plasma at the glomerulus in the same concentration in the water of the glomerular filtrate as in plasma water, that is, approximately in the same concentration as in plasma. If we take the clearance of inulin as the equivalent of the glomerular filtration rate (about 120–130 cc /min) then the product of the inulin clearance, C_{in}, and the plasma glucose concentration, A_{gl} (mg./cc), represents the amount of glucose filtering into the tubular lumina per minute (mg /min). Since the amount normally appearing in the bladder is essentially zero, the filtered amount is completely reabsorbed and that rate of glucose reabsorption, T_{gl}, may be estimated as

$$T_{gl}=C_{in}A_{gl} \tag{21}$$

If the plasma concentration of glucose be raised sufficiently above the "threshold" concentration, the appearance of glucose in the urine is

taken to signify that the tubular reabsorptive capacity has been saturated and that the value of T_{gl} from equation (21) is a *maximum tubular reabsorptive capacity* for glucose with units in mg./min It is symbolized Tm_{gl} Thus,

$$Tm_{gl}=C_{in}A_{gl}-uU_{gl} \qquad (22)$$

On dividing each term on the right-hand side of equation (22) by A_{gl} and also multiplying that whole side by A_{gl}, we get

$$Tm_{gl}=(C_{in}-uU_{gl}/A_{gl})A_{gl}=(C_{in}-C_{gl})A_{gl} \qquad (23)$$

If Tm is constant, then as the plasma level of glucose is increased, the clearance of glucose mathematically approaches that of inulin (Fig 9). Since the inulin clearance may vary where conditions set up by the actual introduction of glucose or some other substance into the body are such as to alter the filtration rate, it may be better said that the ratio C_{gl}/C_{in} approaches 1.

If A_x is the plasma concentration of a substance x, then the rate of tubular reabsorption of x is $C_{in}A_x-uU_x$. The fraction of the filtered quantity which is reabsorbed per minute is $(C_{in}A_x-uU_x)/C_{in}A_x$. Dividing each term by A_x, we have $(C_{in}-C_x)/C_{in}$. For example, if $C_{in}=120$ cc/min and $C_{urea}=75$ cc./min, then $(120-75)/120=0.37$ Thus, 37 per cent of filtered urea is reabsorbed by the tubules in this case.

The *maximum tubular excretory capacity** for a substance like phenolsulfonphthalein (PSP, phenol red) would be represented, by similar reasoning, as

$$Tm_{PSP}=(C_{PSP}-C_{in})A_{PSP} \qquad (24)$$

The force of the formulation of Tm is that where substances are either reabsorbed or secreted in fixed amounts by the tubules, the clearances of those substances tend to approach a glomerular clearance as their plasma concentrations are raised. Concretely this is so because as the plasma concentration increases without limit, the total quantity filtered per minute increases in proportion, becoming indefinitely large The constant tubular increment or decrement (provided by secretion or reabsorption, respectively) pales into insignificance in comparison with the huge glomerular contribution to the bladder urine so that at very high levels of plasma concentration it is as if there were no influence of the tubules at all. As has been indicated previously (§3 11), the clearance of a substance uninfluenced by tubular activity would be at the level of glomerular filtration; and if inulin were excreted at that level, the clearance of the substance in question would approach that of inulin (Fig. 9).

* "Excretory"="secretory" in application to tubular activity

The formulation of equation (24) is not complete Smith, Goldring, and Chasis[1005] who present the method for calculating the rate of tubular secretion give it in the form of

$$Tm_{PSP} = UV_{PSP} - C_{in} A_{PSP} WF \qquad (25)$$

where W is the fraction of water in the plasma and F is the fraction of phenol red (in this case) free in the plasma and filterable The latter fraction is approximately 0 2, the other 0 8 being bound to proteins by adsorption when the total concentration of the dye in human plasma is 1 mg. per cent. When the plasma level of the dye is raised, the fraction of free dye is increased Thus, theoretically, at highest plasma levels, the ratio of the clearance of phenol red to that of inulin should approach the fraction of free dye in the plasma The lowest value recorded for this clearance ratio was 0 89, found in normal man at $A_{PSP} = 28.2$ mg per cent[999]

3 16 *Tubular Transport in Reabsorption and Its Relation to Threshold* With the conception of a maximum reabsorptive capacity for certain substances, one accounts for a threshold concentration merely as a reflection of a Tm of reabsorption since an actively reabsorbed substance which has a Tm will not frankly appear in urine until its plasma concentration reaches such a level that the product of that concentration and the filtration rate (the "load" presented to the tubules) exceeds the Tm for that substance For substances filtered at the glomerulus certain statements can be made which integrate the threshold (of appearance) concentration (§7.2) with other aspects of current renal theory. *(1)* All substances not reabsorbed by the tubules are no-threshold substances, including all secreted substances as well as those eliminated by filtration alone. *(2)* All substances only passively reabsorbed by the tubules are no-threshold substances, for example, urea, and acetone. *(3)* Any nonsecreted substance with a reabsorptive Tm is a threshold substance, all nonsecreted substances which are actively reabsorbed by the tubules are threshold whether or not they have a Tm Thus, glucose, with a Tm, has a threshold and electrolytes like chloride, with no Tm, have thresholds *(4)* Any substance, freely filterable, which ever shows a concentration ratio of less than 1 is a threshold substance

The statement can still be made with reasonable assurance of validity in terms of current renal theory that *any actively reabsorbed substance is threshold if it is not also secreted at a rate equal to or greater than that of its reabsorption; all other substances are no-threshold*

3.17. *Tubular Transport Theory* Shannon[963] proposed a theory of tubular transport based upon the reversible combination which might be formed in the tubular cells between an actively handled solute and some cellular element which is present in constant but limited amount Two consecutive reactions are required:



$$A+B \rightleftharpoons AB \rightarrow Ts+B \qquad (26)$$

where A is the solute at the proximal side of the reaction, in the interstitial fluid around the tubular cells, B is the cellular element, AB is the complex formed reversibly by these two, and Ts is the solute on the distal side of the limiting reaction. It is suggested that the second reaction is a first-order process, its rate being slow in relation to the rate of attainment of equilibrium in the first reaction, in order to arrive at a maximal rate of tubular secretion.* This hypothesis has been provisionally adopted by many renal physiologists although Ekehorn[331] takes exception to it.

3 18 *Competitive Reabsorption and Secretion* The Shannon mass-action hypothesis was proposed to account in part for the mutual depressions and elevations of clearances which have been observed (Fig. 9)

Xylose clearance ordinarily is less than inulin clearance (Table II) and the former is, therefore, said to be reabsorbed. If the plasma glucose concentration is raised from sub- to superthreshold concentrations during xylose excretion, the clearance of the latter rises[960] This phenomenon is consistent with a process of "competitive reabsorption" which could conceivably occur if both substances were transported in the same tubular reabsorptive mechanism. Increased filtration of glucose would deny some of the xylose molecules access to the reabsorptive element common to both substances, on a mass-action basis The clearances of compounds such as sulfamerazine, sulfamethazine, sulfadiazine, sulfathiazole[109], and salicylate[1145] are increased by the administration of sodium bicarbonate or even by other salts such as sodium chloride, ammonium chloride, or potassium chloride, but it is not known whether this type of augmentation is also a manifestation of competitive reabsorption.

The "tubular maximum" hypothesis (§8 1) has been extended to electrolytes Ayer, Schiess, and Pitts[54] suggest two broad categories

* Shannon actually uses the term "tubular excretion" to denote transfer of a preformed substance from interstitial fluid to tubular lumen, as distinguished from the process called "secretion" which may include a change in the chemical constitution of the substance.

of tubular reabsorption for these substances one for those with "fixed" rates of reabsorption, that is, those having *Tm* values (phosphate, sulfate) independent of the filtration rate or the rate of loading of the tubules with the solute; and one for those whose rate of transfer by the tubules is proportional to the filtration rate (sodium, chloride, bicarbonate). These two categories may eventually appear less discrete. The assumption of a *Tm* for sodium which would exist only in the distal tubules[1124] invites the latter view

Among secreted substances phenol red is believed to compete for the same tubular transportation used by diodrast or paraaminohippurate. Just as raising the plasma level of one of these substances has the effect of depressing its own clearance (Fig 9), so can elevated plasma levels of a secreted substance depress the clearance of certain other secreted substances These processes have been reviewed by Smith[1002]. Houck[558] extends the phenomenon of competition to the mutual depression of the glucose *Tm* of reabsorption and the paraaminohippurate *Tm* of secretion observed when the two are determined simultaneously[595] He suggests that in this case the depression is not to be attributed to a competition for a common cellular transport mechanism but rather to a competition for available energy

Unfortunately the elucidation of tubular transport problems is not yet at hand. Potential complexities make the validity of any hypothesis extremely tenuous, and at present the implicit consequences of a particular hypothesis are not all to be surmised Ekehorn[329, 330], for example, entirely rejects the idea that the depression (in man) of creatinine clearances at elevated plasma levels of creatinine need in any way be due to the saturation of a tubular transport mechanism He regards creatinine as a substance normally excreted at the level of glomerular filtration, with minimal if any tubular handling High plasma concentrations of creatinine are considered seriously unphysiological and injurious to the tubules, in consequence of which, they become permeable and permit some of the filtered creatinine to escape from the tubular lumen to the plasma, with a depression of the creatinine clearance to levels actually lower than the inulin clearance. In the rat the clearance of inulin is reduced by elevating the plasma level of paraaminohippurate[667] Shall we conclude only that the glomerular filtration rate is decreased by elevated levels of the latter substance, or are there tenable alternate hypotheses?

3.19. *Tubular Inhibition.* The clearance of penicillin is at the level of the effective renal plasma flow, that is, essentially the same as diodrast or paraaminohippurate, 600–700 cc/min in man Removed

cent via glomerular and 80 per cent via tubular secretion, it is believed to be transported by the same tubular mechanism as the latter substances By raising the plasma concentration of these other substances[110, 882] the penicillin clearance can be diminished, it is thought, by saturating the common tubular transport system.

Beyer and his associates[108, 111, 112] have discovered that the compound carinamide (4′-carboxyphenylmethanesulfonanilide, formerly "*caronamide*") inhibits reversibly the renal tubular transport mechanism for penicillin. The clearance of carinamide itself, corrected for the concentration of the drug, unbound to protein, in plasma water, varies from half to more than twice the creatinine clearance; that is, it is possibly reabsorbed and secreted although its tubular secretion has been questioned. This compound inhibits the tubular transport of phenol red and paraaminohippurate It does not affect the transport of glucose, arginine, or creatinine. These facts have been consistent with the proposal that a separate principle might be involved aside from, or in addition to, the mass-action principle of Shannon, which latter is seen most effectively at high plasma concentration. This separate principle, namely, *tubular inhibition,* which would supposedly operate effectively at low plasma concentrations of penicillin, was considered to involve interference with, and halting of, specific enzymatic processes employed in tubular transport. In any case, carinamide can be used successfully to reduce the rate of elimination of a load of penicillin from the body in order that an antibiotic level might be maintained more effectively.

3 20. *Renal Blood Flow.* In §3 10 it was shown that as a first approximation, the blood or plasma clearance of a substance could be considered the product of the renal blood or plasma flow and the corresponding extraction fraction. It was noted that if a substance were completely extracted from the plasma going to the nephronic or active excretory portions of the kidney, its clearance would be numerically equal to the effective renal plasma flow Due to the existence of known shunts or bypasses taken by some of the blood flow to the ureters, capsule, etc , the question arises as to whether we can be certain that there is 100 per cent extraction from the nonshunted flow White and Heinbecker[1132] determined the actual extraction fraction of diodrast in the dog by sampling arterial and renal venous blood They found that 73 per cent of the diodrast was removed from the arterial blood. This could imply a shunt whose magnitude is 27 per cent of the total blood flow [illegible]d with 100 per cent extraction

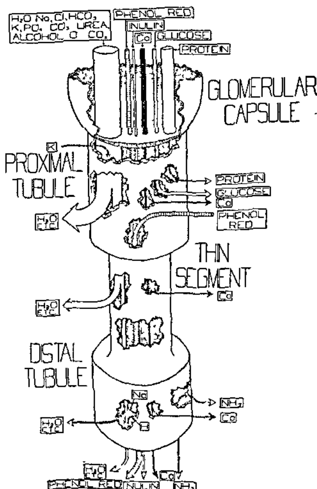


Fig 10 Hypothetical, Nephronic Patterns of Excretion in the Mammal. The locations of potassium and ammonia secretion and of calcium reabsorption are particularly speculative. Water, sodium, chloride, etc. are grouped together since they all are thought to be filtered freely and, in varying degrees, reabsorbed in all segments of the renal tubule. Possible relative contributions to terminal urine, positive or negative, of the four sections of the schematized nephron are indicated roughly by the changes in size of the arrows for individual substances.

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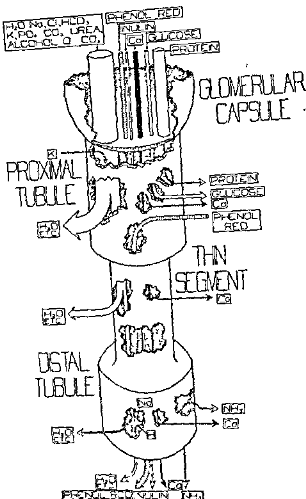


Fig. 10 Hypothetical, Nephronic Patterns of Excretion in the Mammal. The locations of potassium and ammonia secretion and of calcium reabsorption are particularly speculative. Water, sodium, chloride, etc are grouped together since they all are thought to be filtered freely and, in varying degrees, reabsorbed in all segments of the renal tubule. Possible relative contributions to terminal urine, positive or negative, of the four sections of the schematized nephron are indicated roughly by the changes in size of the arrows for individual substances.

from nonshunted flow. However, there is no way to be certain that the nonshunt extraction is complete, although the probability increases as the observed extraction fraction approaches unity. Warren, Brannon, and Merrill[1114], using a long ureteral catheter passed through the antecubital vein into the vena cava and the renal vein, found that the extraction fraction of paraaminohippurate in unanesthetized man averaged 0.88 An extraction fraction of 0 87 has been found in dogs[848]

It is thus likely that under normal conditions the clearances of compounds like paraaminohippurate[1004], diodrast[999], etc. closely approximate at 600–700 cc/min. the effective renal plasma flow. In man the equivalent renal blood flow of approximately 1200 cc/min amounts to perhaps one-quarter of the resting cardiac output Van Slyke[1086] has shown that in the second phase of "shock kidney" where, after prolonged ischemia, restoration of blood flow does not restore renal function, the paraaminohippurate clearance no longer serves to measure renal plasma flow. This type of limitation to clearance-based studies of the renal circulation must be kept in mind[243]. It is not fully known yet what consequences, if any, the Trueta shunts (§3 14, 9 11) will have for the validity of clearance-determined plasma flows.

Van Slyke, Rhoads, Hiller, and Alving[1088] introduced a method for determining *total renal blood flow* in the dog By explanting the left kidney * between the muscle and skin, pedicle intact, they made it possible to obtain blood from a renal vein by subcutaneous needle puncture during a urine collection period. (The ureteral catheter technique of Warren, Brannon, and Merrill[1114], noted above, permits sampling of renal venous blood in man for similar purposes) In their experiments arterial blood was also obtained during this period and midpoint values, approximating the average concentration of urea in the blood during the time of urine formation, were estimated. The formula they used, analogous to the Fick principle for cardiac output determination, was

$$a = \frac{uU}{A - R} \tag{27}$$

where these symbols have meanings previously ascribed (see also Appendix). Equivalent to dividing the clearance of urea by its extraction fraction, this formula permits the calculation of the *total* renal blood flow as opposed to the *effective* renal blood flow, independently of any considerations as to completeness of extraction (§3 10).

* Lockett[679] has given a method for the preparation of bilateral renal explants.

Equation (27) follows from equation (15) in §3.10 which is based on the assumption that the renal venous blood flow equals the renal arterial blood flow. It neglects the diminution in blood flow which should occur as the urine is separated from the circulation. Such neglect results in errors in calculated blood flows which are relatively small for substances with high extraction fractions but which are of considerable magnitude as the extraction fraction becomes small and as the urine flow becomes large[1169]. A paradox is evident for substances that are excreted slowly since a negative flow could be computed from equation (27) alone. It is preferable to derive the total blood flow formula as follows

$$aA=rR+uU \tag{28}$$

where r is the renal venous blood flow

$$r=a-u \tag{29}$$

$$aA=(a-u)R+uU \tag{30}$$

$$a=\frac{u(U-R)}{A-R} \tag{31}$$

Equation (31) differs from equation (27) by the factor $uR/(A-R)$ in which the sub-factor $R/(A-R)$ varies inversely with the extraction

TABLE III

At a urine flow of 1 cc./min. and a given total renal blood flow of 750 cc./min., the expression $R/(A-R)$ is numerically equal to the number of cc. which must be subtracted from the total flow calculated by equation (27) to correct it for the effect of loss of urinary volume from the renal circulation.

Substance Used for Calculation of Flow	$\frac{A-R}{A}$	$\frac{R}{A-R}$
Paraaminohippurate	0 9	0 11
Phenol red	0 5	1 0
Inulin	0 17	4 88
Urea *	0 10	9 0
Protein †	—0 00133	—750

* Urea may at times have a negative extraction fraction, there being more urea in the renal venous blood than in arterial blood[7, 1088].

† It is assumed here that the rate of excretion of protein, uU, is zero.

fraction, $(A-R)/A$. With substances of high extraction fraction, for example, paraaminohippurate, the advantage of equation (31) is negligible, but with substances having extraction fractions like that of inulin

or urea (ca. 0.17 and 0.10, respectively), the errors resulting from failure to use equation (31) can be considerable. Table III indicates how errors grow when the corrected equation is not used. Equation (31) does not allow for the lymphatic loss during passage of blood through the kidney, a correction which is probably small and difficult to estimate. Renal lymph is not derived exclusively from the larger collecting ducts of the kidneys despite the high concentration of urea in that fluid. It is apparently derived from both the renal blood plasma and the tubular reabsorbed fluid[578]

The statement of equation (28), in being more exact than that of equation (14), provides the basic reason why the definition of clearance as the number of cc. of blood virtually cleared of urea in one minute is not a general one In the strictest sense the only correct definitions of clearance thus far considered are (1) the minute rate of excretion of a substance per (its) unit plasma concentration, and (2) the product of the urine volume formed per minute and the average concentration ratio; or any definition which transliterates the clearance formula, $uU/A=C$ (§3.23, 5.2)

3.21. *The Filtration Fraction.* If it be true that the clearance of inulin or thiosulfate[434] or certain other substances is numerically equal to the glomerular filtration rate, and if the clearance of diodrast or paraaminohippurate (PAH) is numerically equal to the effective renal plasma flow, then the ratio of the clearances representing these renal functions, that is, C_{in}/C_{PAH}, is a value indicating the fraction of the effective plasma flow which is filtered off at the glomerulus A normal value in man might be 120/700=0.17 From equation (16) of §3.10 it may be seen that the filtration fraction is approximately equal to the extraction fraction of inulin. The concept of the filtration fraction has been put to use in investigations of the circulatory dynamics of the kidney where, for example, an increased filtration fraction is taken to indicate constriction of the efferent arterioles of the glomeruli with, perhaps, a reduced renal plasma flow in the presence of an essentially normal glomerular filtration rate

3.22. *The Variability of Some Clearance-based Renal Functions* A discussion of the manner in which changes occur in the inulin and diodrast clearances and in Tm values is given by Smith[1002] and will not be pursued here. The inulin clearance in man and dog is relatively

constant. Presumably it changes (proportionately) when the glomerular filtration rate changes, although all conditions under which this may be true have not been certified In disease, where the number of functioning glomeruli is reduced, one finds a decrease in the inulin clearance which makes the determination of this value clinically interesting. Kaplan and Smith[579] found in the rabbit that the inulin clearance increased with increased urine flow and decreased very rapidly with decreased urine flow especially when the latter was small, but no such relationship was seen by Wills and Main[1146]. Chesley [224] showed that with urine flows in man below about 0 35 cc /min. the endogenous creatinine clearance (taken as the glomerular filtration rate) shows a linear dependence on urine flow, suggesting that urine flow is proportional to filtration rate in this range. At normal and high urine flows, the inulin clearance is rather constant, indicating under most conditions[959], but not all[1146], a dissociation of urine flow and filtration rate According to Lassen and Husfeldt[647], glomerular filtration in man (creatinine clearance) is reduced with lowering of systolic blood pressure under spinal anesthesia Oliguria is often found under these conditions

The effective renal blood flow given by the diodrast or paraaminohippurate clearance is somewhat more variable It may be decreased by exercise such as walking[217], and by epinephrine, with concomitant rise in filtration fraction and little change in filtration rate "Psychogenic renal vasoconstriction" during alarm and apprehension has an effect similar in some respects to that of adrenalin injection Spinal anesthesia has no consistent effect on renal circulation[778, 1006] which has made for the claim that the tone of renal arterioles is not maintained by virtue of central nervous system regulation[13] A humoral rather than neurogenic control has been postulated as subserving this end The development of syncope induced by the sustained upright posture is accompanied by a drop in both the diodrast and inulin clearance "Pyrogenic" inulin and pyrexial reactions of other origin give rise to renal hyperemia as evidenced by increased diodrast clearances Disease, again, can lead to marked changes (usually decreases) in effective renal plasma flow; in congestive heart failure renal plasma flow is proportional to cardiac output[773]

The *Tm* of a reabsorbed or of a secreted substance is thought to vary directly as the mass of renal tubular tissue involved in the transport process The incursions of disease or the ablation of renal tubular tissue is reflected in a corresponding diminution of tubular maximum reabsorptive or secretory capacity.

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3 21. *The Filtration Fraction* If it be true that the clearance of inulin or thiosulfate[434] or certain other substances is numerically equal to the glomerular filtration rate, and if the clearance of diodrast or paraaminohippurate (PAH) is numerically equal to the effective renal plasma flow, then the ratio of the clearances representing these renal functions, that is, C_{in}/C_{PAH}, is a value indicating the fraction of the effective plasma flow which is filtered off at the glomerulus A normal value in man might be 120/700=0.17. From equation (16) of §3 10 it may be seen that the filtration fraction is approximately equal to the extraction fraction of inulin The concept of the filtration fraction has been put to use in investigations of the circulatory dynamics of the kidney where, for example, an increased filtration fraction is taken to indicate constriction of the efferent arterioles of the glomeruli with, perhaps, a reduced renal plasma flow in the presence of an essentially normal glomerular filtration rate.

3 22. *The Variability of Some Clearance-based Renal Functions* A [dis]cussion of the manner in which changes occur in the inulin and diodrast clearances and in Tm values is given by Smith[1002] and will not be pursued here The inulin clearance in man and dog is relatively

where both γ and b are known Formula (38) has been used to estimate the volume of distribution of thiosulfate from its clearance[434], and the proportionality between γ and C was demonstrated by Barnett[79] for inulin

3 24 *The "Average" Plasma Concentration* For those substances whose rate of excretion follows the law of exponential decay (§3 8), the plasma concentration of these may also, following a load, decay along an exponential curve (Fig 7). When urine forms in an interval during which plasma concentration is so changing, it is necessary for the computation of a clearance to determine that specific plasma concentration which is representative of the integral and finite urine collection period. This "average" concentration is called "A bar" and symbolized as $\overline{A}$ It can be obtained by a graphic method[1153] in which the exponential curve of serum concentration is plotted against time. The area under this curve is estimated by some appropriate method (for example, planimetry) for the time interval relevant to the clearance period This area is then divided by the abscissal time interval

A method for approximating the average plasma concentration during a period of fall is that of "midpoint interpolation" A rectilinear plot of ln A against time, t, is drawn. The urine collection interval $(t_1 - t_2)$, where t_1 is the beginning of the interval and t_2 is the end, is indicated on the abscissa Where perpendiculars erected from t_1 and t_2 intersect the plotted line, perpendiculars can be dropped to the ordinate at corresponding logarithms of plasma concentrations, ln A_1 and ln A_2. The midpoint of the urine collection interval, t_{mp}, provides by similar construction a corresponding logarithm of midpoint plasma concentration called ln $\overline{A}_{mp}$ The antilogarithm of the latter is $\overline{A}_{mp}$ By plotting the curve on semilogarithmic paper, the value for $\overline{A}_{mp}$ is read directly from the ordinate This approximation to the theoretical $\overline{A}$ is within 1 per cent until A_2/A_1 falls below 0 61 When this ratio is 0 25 the deviation from $\overline{A}$ is 8 per cent; when the ratio is 0 1 the deviation is 19 per cent $\overline{A}$ values are always higher than $\overline{A}_{mp}$ values. By formula,

$$\overline{A}_{mp} = \sqrt{A_1 A_2}$$

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$$\overline{A}_{mp} = \sqrt{A_1 A_2} \tag{39}$$

Although mathematically more rigorous derivations may be given for the proper $\overline{A}$ formula[29], the following is simple and useful The exponential decay equation is equivalent to

$$\ln (A_1/A_2) = \gamma t$$

3.23. *The relation between Clearance and Volume of Distribution.* It is possible to estimate the clearances of certain no-threshold substances without collection of urine. This is consequent to a relation which exists between the clearance of a no-threshold substance and its volume of distribution (§5.2). Derived by Dominguez[305], Wolf[1170], and Newman, Bordley, and Winternitz[810], this relation depends on the fact that the excretion of many substances such as inulin and urea obeys the law of decay (§3.8). When a load of such a substance is being eliminated by the kidneys the following equations are largely valid.

$$A_t = A_i e^{\gamma t} \tag{32}$$

where A_t is the plasma concentration at time t after loading, A_i is the initial plasma concentration upon loading, γ is the velocity constant of excretion, and e is the base of natural logarithms. Thus,

$$\gamma = \frac{\ln (A_i/A_t)}{t} \tag{33}$$

If we plot the natural logarithm (2.303 times the common or Briggsian logarithm) of the plasma concentration against time, a straight line is obtained, after the interval required for mixing of the load in its volume of distribution. That is, the logarithm of the plasma concentration is proportional to time. The slope of this line, easily measured, is the velocity constant, γ. By extrapolating the line to zero time, we approximate there the virtual initial concentration of plasma, A_i, at the initial load, I_i, so that the volume of distribution, b, can be calculated as

$$b = \frac{I_i}{A_i} \tag{34}$$

(Newman et al.[810] suggest using either a normal value for b or determining it by another method. Equation (34) is not equally accurate with substances of differing mixing time and excretion rate.) Since by definition

$$\gamma = \frac{\overline{uU}}{\overline{L}} \tag{35}$$

where the bar means "average," and

$$\overline{L} = \overline{A}b \tag{36}$$

$$\gamma = \frac{\overline{uU}}{\overline{A}b} = \frac{C}{b} \tag{37}$$

$$C = \gamma b \tag{38}$$

excretory mechanism and passage across cells to tubular lumen; and (4) dead space time required for the urine to pass down the tubules, through the pelvis and ureters, to enter the bladder.

TABLE IV

An "A bar" table which can be used to find the average plasma concentration of a substance during a urine collection period in which that substance is removed from the plasma according to the law of exponential decay. Knowing the value A_2/A_1, we can locate the factor $\overline{A}/A_1$ corresponding to it in the table. This factor, multiplied by A_1, gives $\overline{A}$. Delay time must be allowed for separately. See text for details

A_2/A_1	$\overline{A}/A_1$	A_2/A_1	$\overline{A}/A_1$	A_2/A_1	$\overline{A}/A_1$
1.00	1.0000	0.66	0.8182	0.32	0.5968
0.99	0.9951	0.65	0.8124	0.31	0.5892
0.98	0.9904	0.64	0.8067	0.30	0.5811
0.97	0.9858	0.63	0.8008	0.29	0.5736
0.96	0.9791	0.62	0.7949	0.28	0.5656
0.95	0.9754	0.61	0.7890	0.27	0.5575
0.94	0.9701	0.60	0.7830	0.26	0.5493
0.93	0.9642	0.59	0.7771	0.25	0.5410
0.92	0.9590	0.58	0.7711	0.24	0.5325
0.91	0.9543	0.57	0.7650	0.23	0.5239
0.90	0.9500	0.56	0.7589	0.22	0.5151
0.89	0.9439	0.55	0.7527	0.21	0.5062
0.88	0.9385	0.54	0.7465	0.20	0.4971
0.87	0.9336	0.53	0.7402	0.19	0.4877
0.86	0.9282	0.52	0.7340	0.18	0.4782
0.85	0.9228	0.51	0.7277	0.17	0.4684
0.84	0.9176	0.50	0.7214	0.16	0.4584
0.83	0.9124	0.49	0.7149	0.15	0.4481
0.82	0.9071	0.48	0.7085	0.14	0.4374
0.81	0.9016	0.47	0.7020	0.13	0.4264
0.80	0.8963	0.46	0.6954	0.12	0.4150
0.79	0.8909	0.45	0.6888	0.11	0.4032
0.78	0.8853	0.44	0.6821	0.10	0.3909
0.77	0.8800	0.43	0.6753	0.09	0.3779
0.76	0.8745	0.42	0.6686	0.08	0.3643
0.75	0.8691	0.41	0.6617	0.07	0.3497
0.74	0.8634	0.40	0.6548	0.06	0.3341
0.73	0.8579	0.39	0.6478	0.05	0.3205
0.72	0.8523	0.38	0.6408	0.04	0.2982
0.71	0.8467	0.37	0.6336	0.03	0.2766
0.70	0.8411	0.36	0.6265	0.02	0.2505
0.69	0.8354	0.35	0.6192	0.01	0.2150
0.68	0.8297	0.34	0.6118	0.001	0.1446
0.67	0.8241	0.33	0.6043	0.0001	0.1086

where A_1 and A_2 are the respective plasma concentrations at the beginning and the end of a urine collection period. From equation (37) of the previous section

$$\gamma = \frac{\overline{uU}}{\overline{A}b} \tag{41}$$

Combining (40) and (41)

$$\ln (A_1/A_2) = \frac{\overline{uUt}}{\overline{A}b} \tag{42}$$

From (42)

$$\overline{A} = \frac{\overline{uUt}}{\ln (A_1/A_2)b} \tag{43}$$

Independently,

$$\overline{uUt} = (A_1 - A_2)b \tag{44}$$

Combining (44) and (43)

$$\overline{A} = \frac{(A_1 - A_2)}{\ln (A_1/A_2)} = \frac{(A_1 - A_2)}{2\,303 \log (A_1/A_2)} \tag{45}$$

Equation (45) has been used as the basis for table IV where, knowing the ratio A_2/A_1, we can find the value $\overline{A}/A_1$. By multiplying the latter ratio by A_1 we obtain $\overline{A}$ Where plasma concentration is maintained at a fixed level, as during isorrheic infusions (§7.5) of the excreted substance, that plasma concentration is, of course, the "average"

3 25. *Delay Time and Dead Space.* Still another consideration enters into the computation of clearances, particularly over periods in which plasma concentration is changing. Urine, as ordinarily collected from the bladder, is formed not from blood whose composition is that at the moment the extrusion of urine into the bladder occurs, but from blood of a composition existing some time before the extrusion. Thus, a sample of urine forms from blood not of the average composition of "simultaneous" systemic venous (or arterial) blood, but of the average composition existing some time earlier. This time interval was designated by Smith, Goldring, and Chasis[1005] the *total delay time.* It may in some instance be the sum of (1) circulation time from antecubital vein to right heart to renal artery to capillary plexus around the tubules; (2) diffusion time from capillary stream through interstitial fluid, (3) penetration time into tubule cells, reaction with the

CHAPTER IV

Renal Physiology

Osmotic Work; Specific Gravity; Function Tests; Other Studies

4 1. *Renal Energy.* The kidney develops and utilizes energy in various forms *Heat energy* is produced from oxidative reactions, neutralizations, and from physical transfers of materials within the organ, including fluid friction *Work energy* is also developed and employed in physical transfers of water and solutes The secretion pressure of water in the aglomerular fish[116] which may be higher than the hydrostatic pressure of the dorsal aorta (§3 5) is a manifestation of the mechanical work which can be performed by the kidney. Also the distention of the mammalian bladder as urine is forced into it is noteworthy, the minimal work expended being the product of the urine volume and the average tension in the bladder wall, where gravity and ureteral peristalsis do not enter *Electrical energy* is released and can be recorded as a spontaneous electronephrogram (ENG), presumably a function of changes in cellular activity in the renal parenchyma[312] Finally, there is *osmotic work* reflected in and numerically equal to the free energy for different substances which is established with concentration gradients across the tubular wall between plasma and urine, and between each of these and tubular cellular fluid

Osmotic Work

4 2 *The Computation of Osmotic Work* Recognizing the fact that the mammalian kidney is capable of producing a urine whose osmotic pressure may be higher or lower than that of the plasma, many physiologists have sought to express this activity quantitatively Reviewed by Cushny[268], older estimates of osmotic work were based on the relative changes brought about between the plasma and the urine with respect to their over-all composition as indicated by freezing point depressions. Cryoscopy, however, fails to take into account the fact that different substances are on the one hand concentrated in the urine while others are diluted, relative to the plasma.

The latent period in the total delay time other than (*3*), which latter reflects "storage," is called the *minimal excretion time*. This may be estimated by injecting phenol red intravenously and noting the time for its initial appearance in the urine. In man this minimal excretion time for phenol red has been found to be 120 seconds at a urine flow of 20 cc./min., 200 seconds at a urine flow of 1 cc./min.; and about 150 seconds at urine flows of 6 to 2 cc./min.

Gaudino and Levitt[405] use the term *delay time* to represent the interval elapsing between the fall in plasma level and subsequent fall in excretion of a substance like inulin when an infusion, which has previously maintained a constant plasma inulin concentration, is suddenly stopped. The plasma level begins to fall immediately. The product of delay time (min.) and urinary flow (cc./min.) in the dog is a constant, 6 cc. This volume represents a *dead space* containing fluid in that portion of the urinary tract between Bowman's capsule and the bladder.

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Even if we accept some standard method of computing total or fractional osmotic work, there remains the question of its significance for renal function[796, 887]. If the calculations of renal efficiency are based on deficient knowledge of all the paths along which work energy may be diverted and expended, and how these paths vary under differing conditions of renal activity, we are hampered in attaching specific value to that which we calculate The fact that an infinity of functional relations can be drawn between the simple concentration ratio, U/A, and renal activity measured in different ways, makes further suspect the physiological value of the present concept of osmotic work

Consider the concentration of ammonia in urine and plasma First, what kind of plasma shall we take for our equations of osmotic work? Shall it be the systemic venous or arterial plasma whose ammonia is assumed to be 0 000554 mols /kg water by Borsook and Winegarden [151]? Small absolute errors in the determination of this minute value will make for large errors in our final summation of osmotic work, especially where large quantities of ammonia are being excreted Or, shall our concentration ratio be based upon the ammonia content of peritubular capillary plasma? If ammonia (or some other substance) were to be formed de novo in tubular cells and diffuse in such a manner as to cause no concentration gradient between urine and peritubular plasma, we could not regard the tubule as having expended energy in the erection of a concentration gradient Yet when the peritubular blood becomes mixed with that of other tributaries of the kidney having had no contact with ammonigenic tissue, and with the extrarenal systemic blood whose concentration in ammonia is lower than that of the blood among the tubules, there is created a "concentration gradient" which can be used uncritically to assess an imaginary amount of tubular osmotic work It is well to recognize not only that the computations for ammonia require revision[225] but that the free energy contained in a liter of urine is by no means synonymous with a fixed renal energy expenditure implied by the clinically honorific term, osmotic work

Little attention has been given to the *dual* concentration gradients maintained across the urine-tubular cell interface and the plasma

(interstitial fluid)-tubular cell interface or, for that matter, to the effects of "differential permeability"[14], and other germane factors Where $(U-A)$ gradients are zero the integrity of the cell may nevertheless sustain differences in concentration for those substances between its own cellular fluid and both plasma and urine These regions of energy dissipation in osmotic activity may be as real and crucial, or more so, than that region artificially contrived to possess gross $(U-A)$ gradients, as if a single membrane separated urine from plasma. Certainly the computation of zero osmotic work when $U=A$ does not reflect the metabolic energy requirement for the maintenance of the gradients between tubular cell and its urinary and plasma interfaces; and this requirement may, for given gradients, be some function of the combined area of the interfacial membranes

Conceivably the falling maximum urinary concentration of solutes observed in lyuretic diuresis at high solute loads (§8 9) represents a breakdown of the urine-cell concentration gradient, reflecting injury to the cell This could in some degree account for what otherwise seems a discrepancy, that is, that $(U-A)$ falls as A increases. That the tubule cells do not support as high a $(U-A)$ gradient at high A values as at low need not militate, therefore, against the hypothesis of active water reabsorption (§8.9). The assertion that at high absolute U values the limit of osmotic work by the kidney may be approached and that, therefore, $(U-A)$ falls, could of course be merely another way of stating that the gradient at the urine-cell interface metabolically breaks down at certain absolute values of the concentrations involved

4 4 *The Osmotic Limits of Renal Concentration and Dilution.* Compared with distilled water, the freezing point of maximally concentrated urine in man is depressed between 2 2° and 2 6° C, although Cushny [268] states that maximally concentrated urine may not freeze until −5° C is reached The freezing point depression of plasma is 0 56° C

Ordinarily urine has a freezing point of −1° to −2 5° C The total freezing point depression due to salt and urea in maximally concentrated urine is $\Delta=2.2°$ C. In dilute urine, such as forms during water diuresis, freezing point depression has been reported as $\Delta=0.075°$ C. Osmolal concentration is approximated by $\Delta/1.86$, so that for a $\Delta=2.6°$ C, the urine concentration may be expressed as 2 6/1.86 or 1 4 osmolal (§5 2) The validity of this computation is greater where the solutes are nonelectrolytes rather than electrolytes, where the electrolytes are of low rather than high valence, and where the solutions are dilute rather than concentrated.

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4 4 *The Osmotic Limits of Renal Concentration and Dilution.* Com-ared with distilled water, the freezing point of maximally concentrated ırine in man is depressed between 2 2° and 2 6° C, although Cushny [268] states that maximally concentrated urine may not freeze until −5° C is reached The freezing point depression of plasma is 0 56° C. Ordinarily urine has a freezing point of −1° to −2 5° C The total freezing point depression due to salt and urea in maximally concen-trated urine is $\Delta = 2\ 2°$ C In dilute urine, such as forms during water diuresis, freezing point depression has been reported as $\Delta = 0\ 075°$ C Osmolal concentration is approximated by $\Delta/1\ 86$, so that for a $\Delta = 2\ 6$ C, the urine concentration may be expressed as 2 6/1 86 or 1.4 osmol (§5 2) The validity of this computation is greater where the solu are nonelectrolytes rather than electrolytes, where the electrolytes of low rather than high valence, and where the solutions are dil rather than concentrated

physical terminology, osmotic work is called zero on the basis of an algebraic summation of partial work, it is to represent a state of maintained, and not chemical, equilibrium. There must still be a finite expenditure of metabolic energy in the maintenance of this equilibrium, which is not brought to the attention in this mode of analysis.

Even if we accept some standard method of computing total or fractional osmotic work, there remains the question of its significance for renal function[796, 887] If the calculations of renal efficiency are based on deficient knowledge of all the paths along which work energy may be diverted and expended, and how these paths vary under differing conditions of renal activity, we are hampered in attaching specific value to that which we calculate. The fact that an infinity of functional relations can be drawn between the simple concentration ratio, U/A, and renal activity measured in different ways, makes further suspect the physiological value of the present concept of osmotic work.

Consider the concentration of ammonia in urine and plasma First, what kind of plasma shall we take for our equations of osmotic work? Shall it be the systemic venous or arterial plasma whose ammonia is assumed to be 0 000554 mols/kg water by Borsook and Winegarden [151]? Small absolute errors in the determination of this minute value will make for large errors in our final summation of osmotic work, especially where large quantities of ammonia are being excreted Or, shall our concentration ratio be based upon the ammonia content of peritubular capillary plasma? If ammonia (or some other substance) were to be formed de novo in tubular cells and diffuse in such a manner as to cause no concentration gradient between urine and peritubular plasma, we could not regard the tubule as having expended energy in the erection of a concentration gradient. Yet when the peritubular blood becomes mixed with that of other tributaries of the kidney having had no contact with ammonigenic tissue, and with the extrarenal systemic blood whose concentration in ammonia is lower than that of the blood among the tubules, there is created a "concentration gradient" which can be used uncritically to assess an imaginary amount of tubular osmotic work It is well to recognize not only that the computations for ammonia require revision[225] but that the free energy contained in a liter of urine is by no means synonymous with a fixed renal energy expenditure implied by the clinically honorific term, osmotic work

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4.4 *The Osmotic Limits of Renal Concentration and Dilution.* Compared with distilled water, the freezing point of maximally concentrated urine in man is depressed between 2.2° and 2.6° C, although Cushny [268] states that maximally concentrated urine may not freeze until −5° C is reached. The freezing point depression of plasma is 0.56° C. Ordinarily urine has a freezing point of −1° to −2.5° C. The total freezing point depression due to salt and urea in maximally concentrated urine is $\Delta=2.2°$ C. In dilute urine, such as forms during water diuresis, freezing point depression has been reported as $\Delta=0.075°$ C. Osmolal concentration is approximated by $\Delta/1.86$, so that for a $\Delta=2.6°$ C, the urine concentration may be expressed as 2.6/1.86 or 1.4 osmolal (§5.2). The validity of this computation is greater where the solutes are nonelectrolytes rather than electrolytes, where the electrolytes are of low rather than high valence, and where the solutions are dilute rather than concentrated.

specific gravity for each 1 per cent of plasma protein, for example, 0 003×6=0 018 The nonprotein specific gravity of plasma would be 1 028−0 018=1 010 Since some constituents in the urine may be more and others less concentrated than in plasma, it may be illusive to accept the occasion of any urinary specific gravity of 1 010 as indicative of complete renal insufficiency. However, as isosthenuria develops with renal insufficiency as indicated by concentration-dilution tests (§4 12), this interpretation of the isosthenuric point probably takes on more significance. It is properly cautioned[646] for clinical purposes that the urinary specific gravity should be corrected for protein which may be present by subtracting 0 003 units from the

TABLE V

Specific gravity of aqueous solutions of glucose *

Per Cent *d* Glucose	$D^{25°}_{4°}$
1.00	1 0007
2 11	1 0051
4.36	1 0146
10 20	1 0370
15.72	1.0604
20 14	1 0795
24 03	1 0962

* From International Critical Tables, Vol. II, p 347, 1927. Courtesy of McGraw-Hill Book Company

specific gravity for each 1 per cent protein found therein. The baruria resulting from the presence of glucose in the urine has no established "correction" (Table V) Apparently glucose or sucrose in the urine lowers the maximal urinary concentration of electrolytes[393, 537]

4.7 *Some Quantitative Aspects of Urinary Concentration and Composition.* The term specific gravity (relative density), as applied to urine, usually refers to the ratio of the weight of any volume of urine to the weight of an equal volume of water either at the same temperature or at the temperature at which the density of water is maximal, namely 4° C. Symbolically, these urinary (U) specific gravities are represented as $(D^{T°}_{T°})_U$ and $(D^{T°}_{4°})_U$, respectively. The latter is numerically equal to the density of the urine at $T°$ C. Solid substances of greater density than water will, when dissolved in water, cause the relative density of the resulting fluid to exceed that of water by an amount called the *specific gravity increment.* The increments for $(D^{T°}_{T°})_U$ and $(D^{T°}_{4°})_U$ are, respectively, $[(D^{T°}_{T°})_U-1]$ and $[(D^{T°}_{4°})_U-(D^{T°}_{4°})_{H_2O}]$, where $(D^{T°}_{4°})_{H_2O}$ is the density

of water at T° C. Urinary specific gravities, determined at 20° C. and referred to water at 4° C. thus have increments approximately by $[(D^{20°}_{4°})_U - 0.9982]$.*

If urine is diluted with water, the specific gravity increment varies inversely with the degree of dilution. Where a small sample of urine is diluted n-fold with water to permit a determination of specific gravity, $(D^{20°}_{4°})_{U'}$ on the larger volume of urine U', the specific gravity, $(D^{20°}_{4°})_U$, of the original urine sample U would be given by

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or,

$$(D^{20°}_{4°})_U = n[(D^{20°}_{4°})_{U'} - 0.9982] + 0.9982 \quad (50)$$

To find $(D^{15°}_{15°})_U$, where the specific gravity of the diluted urine is $(D^{15°}_{15°})_{U'}$, we would have

$$(D^{15°}_{15°})_U = n[(D^{15°}_{15°})_{U'} - 1] + 1 \quad (51)$$

The obvious correlation between the specific gravity of the urine and the quantity of dissolved material it contains in a unit volume has inspired a number of methods for functionally relating these.† They all involve the use of "coefficients," among the oldest of which are those of Trapp and of Häser[499]. Trapp's coefficient was 2. A urinary specific gravity of 1.010 was regarded as if it were numerically 1010, and the "formula" of Trapp consisted of subtracting 1000 from the latter and doubling the difference. The result, 2×10=20, was taken to equal the number of grams of total solid per liter of urine. Häser introduced the coefficient 2.33 to be applied in place of Trapp's coefficient, contending that it gave more accurate results. Vogel[499] considered Trapp's coefficient more exact for close-to-normal urine, and Häser's coefficient better for urine containing sugar.

Later, Long[687] measured the solids in fresh urine from normal individuals and obtained what he called a "Häser coefficient" by dividing the second, third, and fourth decimal places of the specific gravity into the weight of solids contained per liter. When the specific gravity was taken at 25° C. and referred to water at 4° C., this coefficient averaged 0.260. In using this coefficient with a urine of specific gravity 1.0215, we would calculate 0.260×215=55.90 grams of total urinary solid per liter.

The use of these factors to estimate the approximate quantity of material dissolved in the urine does not prove uniformly good with urines of random composition. In normal subjects on fixed diets the

*0.9982 = $(D^{20°}_{4°})_{H_2O}$, the density of water at 20° C.

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specific gravity for each 1 per cent of plasma protein, for example, 0 003×6=0 018 The nonprotein specific gravity of plasma would be 1.028−0 018=1 010. Since some constituents in the urine may be more and others less concentrated than in plasma, it may be illusive to accept the occasion of any urinary specific gravity of 1.010 as indicative of complete renal insufficiency. However, as isosthenuria develops with renal insufficiency as indicated by concentration–dilution tests (§4.12), this interpretation of the isosthenuric point probably takes on more significance. It is properly cautioned[646] for clinical purposes that the urinary specific gravity should be corrected for protein which may be present by subtracting 0.003 units from the

TABLE V

Specific gravity of aqueous solutions of glucose *

Per Cent *d*-Glucose	$D_{4^\circ}^{25^\circ}$
1 00	1 0007
2 11	1 0051
4 36	1 0146
10 20	1 0370
15 72	1.0604
20 14	1.0795
24.03	1 0962

* From International Critical Tables, Vol. II, p. 347, 1927 Courtesy of McGraw Hill Book Company.

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4 7 *Some Quantitative Aspects of Urinary Concentration and Composition.* The term specific gravity (relative density), as applied to urine, usually refers to the ratio of the weight of any volume of urine to the weight of an equal volume of water either at the same temperature or at the temperature at which the density of water is maximal, namely 4° C. Symbolically, these urinary (U) specific gravities are represented as $(D_{T^\circ}^{T^\circ})_U$ and $(D_{4^\circ}^{T^\circ})_U$, respectively The latter is numerically equal to the density of the urine at T° C Solid substances of greater density than water will, when dissolved in water, cause the relative density of the resulting fluid to exceed that of water by an amount called the *specific gravity increment.* The increments for $(D_{T^\circ}^{T^\circ})_U$ and $(D_{4^\circ}^{T^\circ})_U$ are, respectively, $[(D_{T^\circ}^{T^\circ})_U-1]$ and $[(D_{4^\circ}^{T^\circ})_U-(D_{4^\circ}^{T^\circ})_{H_2O}]$, where $(D_{4^\circ}^{T^\circ})_{H_2O}$ is the density

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If urine is diluted with water, the specific gravity increment varies inversely with the degree of dilution. Where a small sample of urine is diluted n-fold with water to permit a determination of specific gravity, $(D_{4°}^{20°})_{U'}$ on the larger volume of urine U', the specific gravity, $(D_{4°}^{20°})_{U}$, of the original urine sample U would be given by

$$(D_{4°}^{20°})_{U}=n[(D_{4°}^{20°})_{U'}-(D_{4°}^{20°})_{H_2O}]+(D_{4°}^{20°})_{H_2O} \qquad (49)$$

or,

$$(D_{4°}^{20°})_{U}=n[(D_{4°}^{20°})_{U'}-0.9982]+0.9982 \qquad (50)$$

To find $(D_{15°}^{15°})_{U}$, where the specific gravity of the diluted urine is $(D_{15°}^{15°})_{U'}$, we would have

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4.36	1.0146
10.20	1.0370
15.72	1.0604
20.14	1.0795
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of output of water augments more than that of other substances[16].

The high specific gravity (baruria) which may be obtained during water restriction and oliguria in normal individuals under uniform conditions is used as a standard in so-called "concentration tests" of renal function (§1.12). "Dilution tests," similarly, may be based on the normal response to water freely taken or forced. Urinary specific gravity under these conditions commonly approaches that of pure water (for example, where $(D^{T}_{T})_{H_2O} = 1\,000$, we may find $(D^{T}_{T})_U = 1.001$). Such dilute urine, flowing profusely, characterizes the state of *hydruria* In general the rate of excretion of dissolved materials is greater at high urine flow than at low [268, 1013] but there are exceptions to this (§8.7).

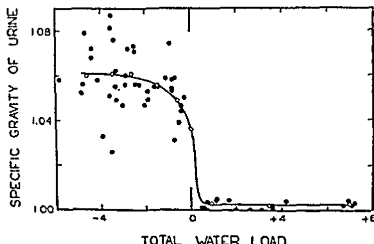


Fig 15. Specific Gravity of Urine in Relation to Total Water Load (per cent of body weight). Dogs on constant diet. Each black dot represents a separate day, in negative loads, 3 individuals deprived of water, in positive loads, 2 other individuals given water repeatedly by stomach. Each white dot represents a mean specific gravity for a 1 per cent interval of load. After Adolph [16]

4 8. *Urinary Specific Gravity as a Function of Age.* In normal men over 40 years of age it has been demonstrated by Lewis and Alving[658] that the concentrating ability of the kidney, as measured by the specific gravity of the urine during restricted water intake (concentration test), falls from 1.030 at 40 years to 1.023 at 89 years They submit an equation of regression

$$\text{Nonprotein specific gravity} = 1.036 - 0.00015A \qquad (55)$$

tonic solutions of urea, chloride, or phosphate is accompanied by a lowering of the specific gravity of the urine In diuresis induced by solutions of sodium sulfate of comparable concentration, specific gravity can actually be increased[775]. The functional relation between specific gravity and the urine flow, depending complexly as it does upon the particular substances calling for excretion, is less informative physiologically than that between urinary concentrations for individual substances and the urine flow, although even the latter interdependence is occasionally baffling

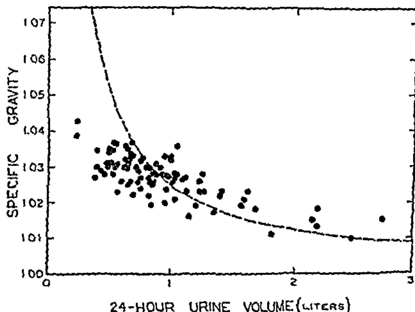


Fig. 12. Relation between Urinary Specific Gravity and Daily Urine Volume. Each point represents one measurement made in desert conditions Most of the subjects were soldiers The broken line is a hyperbola passing through the mean of all points. On this hyperbola occur equal excretions of total solutes in diverse urinary volumes. After Adolph and Associates [20].

Urinary specific gravity, as a function of urinary flow, is closely related to the body's water load (Fig. 12, 13). A single measurement of urinary specific gravity may do more to identify the existence of a water increment than any other single measurement. Curiously enough, in positive water loads, samples of urine vary around one concentration and in negative water loads around another, with a steep transition between (Fig. 13). Concentrations of many urinary constituents (chloride, urea) correlate similarly with water load. It may be concluded that where loads of water alone give rise to water diuresis, the rate

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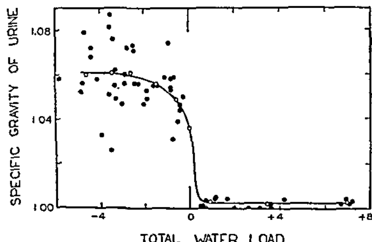


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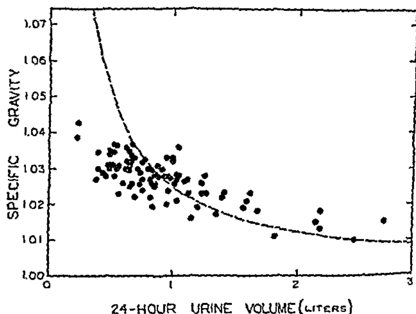


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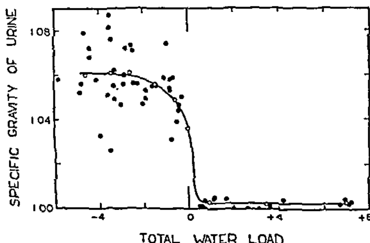


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where A is the age in years Howell and Piggot[560] do not find the drop in specific gravity proportional to the age in years in men over 65. The volume of urine *excreted during restricted water intakes* is similar in men of different ages.

The urine of newborn infants is markedly hypotonic with respect to the plasma although in the first two days of extrauterine life infants ordinarily excrete a comparatively concentrated urine (400 milliosmolar compared with plasma at 300 and with adult urines from 600 to 1300 or 1400 milliosmolar) From the third to sixth day in infants there is a decrease in urinary concentration which seems to be correlated with the volume of fluid intake[518]. Despite small urine volumes ranging from 16 cc per 24 hours on the first day of extrauterine life to 200 cc per 24 hours on the sixth day, the specific gravity is no higher than 1 012 on the first day and decreases to about 1 003 or 1.004 on the sixth[995] By adult standards the osmotic pressure and concentration of infant urine are defective, but they may rise to adult levels when the serum composition is highly abnormal[744]

4 9 *Experimental Hyposthenuria* Hayman, Shumway, Dumke, and Miller[505] have reveiwed the literature of hyposthenuria and studied several aspects of experimental hyposthenuria in the dog After kidney denervation urinary flow is increased and the specific gravity under concentration test is diminished Decreasing the renal mass by any of a number of applicable techniques also results in polyuria and hyposthenuria These are thought to be adequately explained by relatively increased blood flow and greater volume of glomerular filtrate to the remaining glomeruli, resulting in a more rapid flow of fluid down the tubules, with decreased time for tubular reabsorption Where renal mass is reduced, the antidiuretic influence of pitressin does not bring about a higher urinary specific gravity than does water deprivation *Urinary solute concentration is not high*, so this is not the limiting factor. Dogs with subtotal nephrectomy can excrete a concentrated urine, however, under certain conditions These include increased concentration of plasma colloids, low blood pressure, and injections of sodium sulfate after water deprivation Thus, there may be no need to postulate tubular damage under these conditions On the other hand, tubular damage, as from uranium poisoning or ureteral obstruction, constitutes a separate category of hyposthenuria. *Hyposthenurias* are classified as *tubular* and *nontubular*, the former including all definite tubular degenerations and the latter, reductions in renal mass. No *definite category is given for the hyposthenurias* of denervation, low

protein diet, and of pregnancy. The ordinarily lower urinary specific gravity of pregnancy, labor, and the postpartum period are correlated with larger than normal urinary volumes

Renal Function Tests

4 10 It is not within the province of this book to deal at length with renal function tests whose number is legion and which bear empirically for the most part on problems of renal pathology. Potentially, an almost infinite number of procedures might be adapted to serve as "function tests" with more or less success Yet, of the large number actually proposed only relatively few have stayed on. These endure because of their clinical procedural simplicity, reliability, and apparent physiological significance. They are needed because of the unreliability of certain direct observations which may be highly suggestive For example, albumin and casts may be absent from urine in severe renal disease yet they may be present when there is no primary kidney disorder[917] Quantitative renal function tests in common use today may be grouped roughly as tests of *retention, concentration-dilution, excretion*, and *clearance*

4 11 *Retention Tests.* When the kidneys are unable to excrete certain body solutes in normal quantities, at normal rates, or with the normally increased rates which characteristically follow the creation of solute loads, there is a retention of these materials relative to the body water content, and an increase in their plasma concentrations can often be demonstrated Urea nitrogen, nonprotein nitrogen, creatinine, hydrogen ion, etc , are among those substances whose abnormal plasma levels are taken to indicate renal insufficiency * † Of course, plasma

* The normal concentration of blood urea nitrogen (BUN) is said to vary with age[658] from 12 mg. per cent at 40 years to 18 mg per cent at 89 years, the regression equation being

$$\text{BUN (mg per cent)} = 7.56 + 0.112A \qquad (56)$$

where A is age in years Howell and Piggott[560] find no change in blood urea in persons over 65 years of age.

† Abnormal retention is reflected in other body fluids than plasma. Hench and Aldrich[531] find that the blood urea nitrogen is paralleled in the saliva by the combined salivary nitrogen of urea and ammonia. Urea enters the saliva largely by diffusion but a certain fraction of that urea is hydrolyzed (depending partly on the condition of the mouth) with the formation of ammonia In children or other persons difficult to bleed, the salivary combined nitrogen may be used in place of the blood urea nitrogen for diagnostic purposes

concentration of solute reflects a state of load rather than a state of renal excretion of solute, when body content of water is normal. Rapid intake of acid-forming salt such as ammonium chloride causes at least temporary acidemia even in normal persons despite elevated excretion of urinary acid Serum urea varies importantly with dietary consumption of protein. In 10 healthy men average serum urea concentrations were found to be 13, 23, 36, and 43 mg. per cent, corresponding to protein consumptions of 0.06, 0 5, 1 5, and 2 5 g /kg.[4]. Thus, a serum urea level of 50 mg. per cent might be normal for a high protein intake

In view of these and related facts, high plasma levels are occasionally distinguished as primarily *renal* (as in disease of the kidney), *prerenal*, or *postrenal*. Prerenal azotemia, for example, arises not only from elevated intake of nitrogen but with factors affecting tissue metabolism It has been used to include renal dysfunction, but not necessarily on a morphological basis[367], as in widespread burns with shock, surgical shock, hyperemesis gravidarum, etc. Postrenal azotemia may follow urologic obstruction. It has been said that in renal insufficiency, the substances with normally high concentration ratios are most prominently retained. This should be qualified on at least two counts. First, a substance like potassium which is capable of being highly concentrated (Table II) by the normal kidney[1154, 1173] is not markedly retained in many renal dysfunctions[585] and second, substances like sodium and chloride, which show low concentration ratios, may be retained along with water in edema fluid though without a significant increment in concentration

4 12. *Concentration-Dilution Tests.* When the body is deprived of water for a period exceeding several hours the specific gravity of the urine rises, constituting a reproducible physiological reaction (Fig 14). In renal insufficiency where there is tubular dysfunction, the specific gravity does not rise under this concentration test to so great a degree as in the normal The specific gravity provoked, if below an empirically determined value (for example, 1 026 in average men), can be taken as an indication of tubular damage Conversely, when the body is positively loaded with water the specific gravity of the urine normally falls (Fig 13), along with an increase in urinary flow (Fig 37). This also is a physiological reaction depending on tubular integrity In severe renal disease the urine, whether formed under conditions of water deficit or excess, tends to remain at a rather uniform specific gravity, in the neighborhood of 1.010, and the degree of this isosthenuria measures rather reliably the degree of insufficiency

Pituitrin has been employed to facilitate the concentrating power of the kidney[192]. In dogs restricted of food and water for 18 hours prior to a test, the administration of surgical pituitrin results in the formation of a more concentrated urine than occurs following restriction of water alone[832]. The average specific gravity has been found to rise from 1.038 without pituitrin to 1.049 with the drug. The specific gravity of dog's urine *is greater than that of human urine under comparable conditions* of water deprivation (Figs 12, 15).

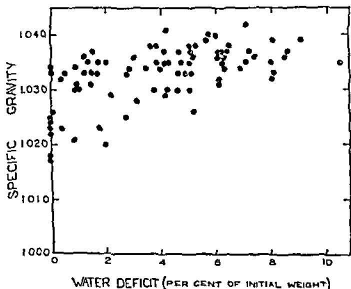


Fig. 14 Relation between Urinary Specific Gravity in Man and Body Water Deficit. *After* Adolph and Associates [20]

In man pituitary hormone is reported to produce a baruria equal to or in excess of that obtained by simple water deprivation[1012, 1111]. This is especially true in cases of cardiac edema where fluid from the edema may enter the urine and prevent the attainment of a specific gravity as high as would otherwise occur in a simple concentration test. However, some workers[1049] find that simple dehydration gives less variable and higher average specific gravities than pitressin, and that the specific gravity "ceiling" is not reached with pitressin. Pasqualini [838] uses the lack of normal antidiuretic response to pitressin as a measure of renal dysfunction, rather than the concentration response.

Alving and Van Slyke[30] have evaluated the significance of concentration and dilution tests in Bright's disease. They find that the

similar to those of the MUC during changing states of hydration, solute load, hormonal influence, etc. But neither the MUC nor the maximum specific gravity can be used to measure purely "physiologic" renal function because they are obtained under metaphysiologic (§1.6) conditions which, if maintained, lead to death. It would be of some interest if it could be established that the higher of two specific gravities obtained under concentration test in two different, normal individuals implied greater physiologic reserve Such a relation has a certain *intuitive appeal but no current renal theory justifies prediction of its* existence (§7.8, 7.10)

4.13. *Excretion Tests* The defective urinary excretion of dyes in certain renal diseases[917, 918] has been recognized since Achard and Castaigne[3] introduced the methylene blue test into medicine. Rowntree and Geraghty[918], however, showed the superiority of phenolsulfonphthalein ("phthalein", PSP, phenol red) as a test substance and set forth one of the simplest and most useful renal function tests known

When a fixed dose of phenolsulfonphthalein (6 mg. in 1 cc) is injected intravenously its prompt excretion, primarily by tubular secretion, sets in according to the law of exponential decay. In normal man it is found that 40 to 60 per cent of the injected quantity is excreted within one hour. An additional 20 to 25 per cent is eliminated in the second hour Marked diminution in this normal rate of excretion suggests the presence of renal disease, primarily tubular * Because a standard dose of dye is used in the phenolsulfonphthalein test it may be assumed that in normal individuals this raises the plasma concentration close to some average value. This implies that variations in the measured rate of excretion correspond in a way to variations in *the clearance of this material* †

* The glomerular and tubular partitioning of phenol red may be given as follows[999]: phenol red is adsorbed on plasma protein such that at a total plasma concentration of 1 mg per cent about 20 per cent of the dye is free and filterable At a glomerular filtration rate of 120 cc./min, the *glomerular clearance* of dye would be $120 \times 0.2 = 24$ cc./min The *total renal clearance* of phenol red is 400 cc./min. The *tubular clearance* is, therefore, $400 - 24 = 376$ cc/min Thus, the

(measured by per cent excreted per unit time) for the elimination of phenol red ... do adults, when intramuscular injections are given[436]

4.14 *Clearance Tests* These tests, from the physiological and clinical viewpoints, have been treated at length in many places[222, 223, 787, 999, 1002]. A clearance test is essentially a combination of a retention test and an excretion test in that it measures a *rate of excretion per unit plasma concentration* First employed in connection with urea[787], the clearance determination was rapidly extended to other substances as its curious mathematical properties suggested many physiological applications (Chapter III).

As has been mentioned (§3 12), the clearances of certain substances such as inulin, urea,* creatinine, or mannitol may closely parallel the glomerular filtration rate and, within limits,† may be used as specific or relative[1153] tests of glomerular function Clearances of other substances such as phenol red, paraaminohippurate, and diodrast presumably reflect tubular function for the most part and with proper standardization they may be so interpreted The *Tm* (§3 15), another clearance-based value, has also been used to provide information on renal tubular activity. These, together with the previously mentioned (Chapter III) determinations of effective renal blood flow and filtration fraction have brought the clearance into considerable prominence as a tool for the study of renal function

It is possible, however, for tests to become so elaborate that one loses track of simpler, equivalent measures of renal function. Corcoran

* The "clearance of urea" as a renal function test refers to the value of uU/A for urea at urine flows above the augmentation limit (§3 9) of 1 to 2 cc./min. in man Moller, McIntosh, and Van Slyke[787], who originally introduced the term "clearance," called the formulation uU/A the "maximum clearance" of urea because it appeared to reach no higher value than about 75 cc/min. with increasing urine flow above the augmentation limit In seeking to apply this function test at lower urine flows than the augmentation limit, such as might be found in children, they made use of the empirical finding[52] that at small urine flows, between the "minimal" urine flow of 0 35 to 0 5 cc./min.[222-224] and the augmentation limit, the rate of excretion of urea per unit plasma concentration was proportional to the square root of the urine flow, that is

$$\frac{uU}{A}=C_s\sqrt{u} \tag{57}$$

and

$$C_s=\frac{\sqrt{u}U}{A} \tag{58}$$

where C_s was a constant in normal individuals, numerically equal to 54 This was called the "standard clearance" and deviations from the average value of 54 were used to assess the state of renal function Dimensionally the standard clearance is not a clearance at all and has none of the latter's theoretical significance

† Except, for example, where tubular permeability is so increased by "injury" as to result in decrements in the clearances from passive reabsorption.

similar to those of the MUC during changing states of hydration, solute load, hormonal influence, etc. But neither the MUC nor the maximum specific gravity can be used to measure purely "physiologic" renal function because they are obtained under metaphysiologic (§1.6) conditions which, if maintained, lead to death. It would be of some interest if it could be established that the higher of two specific gravities obtained under concentration test in two different, normal individuals implied greater physiologic reserve. Such a relation has a certain intuitive appeal but no current renal theory justifies prediction of its existence (§7.8, 7.10).

4.13. *Excretion Tests* The defective urinary excretion of dyes in certain renal diseases[917, 918] has been recognized since Achard and Castaigne[3] introduced the methylene blue test into medicine. Rowntree and Geraghty[918], however, showed the superiority of phenolsulfonphthalein ("phthalein", PSP, phenol red) as a test substance and set forth one of the simplest and most useful renal function tests known.

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† By way of qualification, phenol red excretion is 10 to 13 per cent greater in the recumbent than in the erect position[245]. It is less rapid in age, less rapid in the presence of some cardiac diseases, and more rapid in children[367] if it is given intravenously. Even the youngest infants and children show about the same capacity (measured by per cent excreted per unit time) for the elimination of phenol red as do adults, when intramuscular injections are given[436].

and decreases the polyuria Water diuresis cannot be produced in the isolated kidney[1166]

The urine of the isolated kidney is ordinarily free from glucose but with administration of hydrocyanic acid or sodium cyanide which poison and suspend tubular activity, it appears This type of tissue poison leads to some diuresis with the excretion of almost, but not quite, a pure glomerular filtrate[89, 326, 466, 1026] Starling and Verney[1026] considered the fall in concentration and rate of excretion of urea in the cyanide-perfused kidney as evidence for the tubular excretion of this substance It might be supposed, in more modern terms, that cyanide poisoning should institute a diuresis approaching in magnitude the glomerular filtration rate since the active reabsorption of water and sodium, among other substances, would be depressed. Yet urine flow does not increase much In the intact rabbit, potassium cyanide poisoning leads to a decreased urine flow[678] No satisfactory resolution of this problem has yet been made despite the contention of Richards and Barnwell[896] that poisoning of the renal tubules by cyanide should not produce diuresis because the permeability of the tubules would be increased and tubular fluid would tend to be reabsorbed by the effective osmotic pressure of plasma proteins. The volume of fluid moved thus passively in the poisoned kidney is supposed, in this view, to equal that reabsorbed in the normal kidney.

Phlorizin will also poison the tubules of the isolated as well as the intact kidney, interfering with glucose reabsorption Complete interference is obtained by a dose of 0 5 to 1 0 mg per gram of kidney. How phlorizin acts on the glucose reabsorption mechanism is uncertain, disturbance of phosphorylation processes having been ruled out since the concentration of phlorizin effective in the kidney is probably lower than that necessary to inhibit esterification in muscle pulp and yeast[692, 999] Phlorizin also lowers the ability of tubules to excrete diodrast[1127] and creatinine Shapiro[970] believes it necessary to assume that inhibition of susceptible dehydrogenase systems is the primary basis of phlorizin action in the kidney Action of phlorizin on glucose utilization and phosphorylation are considered secondary to the inhibition by the drug of the production of high energy phosphate bonds He assumes that phlorizin acts primarily on dehydrogenase systems that are coupled with phosphorylation The inactivation of high energy phosphate bonds by phlorizin fits in with the idea that such bonds are important in renal function for other purposes than glucose reabsorption

Conway, Fitzgerald, and MacDougald[238] suggest that after phlorizin administration, glucose is secreted by the tubules in the frog (§3 13)

and Page[241] studied the relations among urinary specific gravity, urea clearance, and diodrast *Tm* and concluded that it was possible to calculate the latter in terms of the other two. That such correlations exist excites inquiry into the supposedly fundamental nature of any of these factors and calls for the greatest simplification of renal theory compatible with the facts

Perfused, Isolated, and Artificial Kidneys

4.15 In addition to the methods considered so far which permit the study of renal function in the intact animal, there are others used by physiologists which have attained importance These latter include perfusion of the kidney in situ as practiced by Hooker[555] and by Richards and Plant[897], perfusion of the so-called "isolated kidney[89, 530, 858, 1026, 1100, 1160], and autoperfusion of artificial kidneys[2, 31, 610, 801, 991]. The latter may be used in conjunction with intact kidneys or substituted for the natural organs when these have been removed from the practice of physiological regulation either through design or disease. These methods do not constitute a strictly homogeneous group but are considered here together because they are, in common, powerful and direct and they can be used to enrich our understanding of renal and extrarenal regulations.

4.16 *The Isolated Kidney.* An isolated kidney is one arranged mechanically to receive freshly defibrinated blood,* oxygenated by the lungs and circulated either by means of the heart (heart–lung–kidney) or a pump (pump–lung–kidney) It is a preparation which can be made to function at constant blood flow or blood pressure, constant urine flow or ureter pressure, or chosen values of these. Furthermore, it produces an abundance of urine which is usually markedly hypotonic to blood serum[323, 530, 1026, 1137, 1166].

Urea and sulfate are present in greater concentration in such urine than in the serum whereas chloride usually has a concentration ratio much below one This is attributed to the fact that the isolated kidney does not ordinarily receive the circulating antidiuretic and oxytocic principle supplied by the pituitary gland. Pituitrin, when added to the circulation of an isolated kidney, raises the concentration of chloride in the urine (though it may[268] or may not make it hypertonic)

* A toxic and vasoconstrictor substance, which can prevent perfusion of blood through the isolated kidney, is apparently supplied by the kidney itself[822] and detoxified by the lungs[1026]

when the ureteral and venous pressures are so chosen that, taken one at a time, they produce the same reduction in urine flow. The derivation of this formulation depends on the assumption that both ureteral and venous pressures act solely by reducing the rate of glomerular filtration, shown to hold true for venous pressure but not exactly for ureteral pressure

Re-examination of the relations among renal pressures by Eggleton, Pappenheimer, and Winton[324] led to modified pressure equations. Equation (59) becomes

$$\frac{\text{absolute glomerular pressure}}{\text{absolute arterial pressure}} = \frac{\text{increase in ureteral pressure}}{\text{increase in venous pressure}} \qquad (60)$$

where the increases are applied one at a time and so chosen that they produce equal changes in the glomerular filtration rate Further,

$$\frac{\text{absolute glomerular pressure}}{\text{absolute arterial pressure}} = \frac{\text{increase in ureteral pressure}}{\text{increase in arterial pressure}} \qquad (61)$$

where the increases are applied simultaneously and so chosen that there is no change in the glomerular filtration rate; and

$$\text{increase in venous pressure} = \text{increase in arterial pressure} \qquad (62)$$

where the increases simultaneously applied produce no change in glomerular filtration rate or in the urine flow

The intrarenal (intracapsular) pressure, normally 4 to 14 mm mercury (average 10) in the isolated kidney of the dog, is raised by diuretics like sodium sulfate, urea, and glucose At the same time the volume of the kidney increases, a result which may also be produced by increase in blood flow, ureteral pressure, venous pressure, or by a decrease in extrarenal pressure There is evidence that intrarenal pressure obstructs the outflow of urine by exerting a lateral pressure on some part of the tubules, as where a diuresis is produced by lowering the pressure below atmospheric, in a chamber enclosing the kidney Urine flow increases proportionately with the reduction in extrarenal pressure until a certain critical pressure of about −10 mm mercury, at body temperature, is reached[535] It is believed that the polyuria coming from one-half of a kidney, induced by a ligature of the branch of the renal artery supplying the other half, may be due to reduction in intrarenal pressure associated with the change from a relatively tense to a flaccid condition[857, 858, 1166]

Winton[1166] shows that the idea of intrarenal pressure as an important property of a kidney developed more or less independently

4.17. *Intra- and Extrarenal Pressures.* Urinary secretion normally takes place only when certain conditions are met concerning arterial, glomerular, venous, ureteral, intrarenal (intracapsular), and extrarenal (oncometric or abdominal) pressures The study of these pressures is complex and far from complete. Lépine and Porteret[654] early studied urine secretion against elevated ureteral pressures In dogs with cannulated ureters it was determined that urine flow could be decreased to about 6 per cent of normal at 33 mm. mercury, and finally stopped at higher pressures. In anesthetized dogs the normal, "resting," maximum, ureteral pressure is now given at about 30 mm mercury[1166]. It may be raised by diuretics such as urea, sulfate, and sucrose to 70 mm mercury

The interrelations of ureteral and other renal pressures have most carefully been worked out by Winton and his co-workers[114, 323, 324, 535, 969, 1160–1162, 1164–1166] using the isolated mammalian (dog) kidney. There is no regular change in the renal blood flow as a result of increased ureteral pressure up to 20 mm mercury which, they find, almost abolishes urine flow. Presumably the pressure in Bowman's capsule is increased, retarding the production of intracapsular fluid; little influence on tubular activity is detected

When venous pressures are raised by obstruction[1161] two factors act in opposite directions· *(1)* venous pressure is transmitted to fluid in the distal portions of tubules and so retards the secretion of urine in the same way as does pressure applied to the ureter; *(2)* a fraction of the pressure in the vein is transmitted back along the blood vessels, raises the pressure of the glomerular capillaries, and so accelerates the secretion of urine in the same way as does a small increase of arterial pressure. This increment in glomerular pressure, subtracted from the total increase in venous pressure, should therefore yield a pressure which when applied to the ureter (the vein being unobstructed) would induce the same reduction of urine flow as that due to application of the venous pressure (the ureter being unobstructed). As with increased ureteral pressure, venous obstruction has no appreciable influence on the activity of tubules, as judged from the observation that urea and chloride (two substances presumably handled by different tubular mechanisms) are affected no differently in their urinary concentrations than normally. These and other considerations led Winton[1162] to originate a rule stating

$$\frac{\text{glomerular pressure}}{\text{arterial pressure}} = \frac{\text{ureteral pressure}}{\text{venous pressure}} \qquad (59)$$

in three sets of circumstances First, the observation of surgeons[494] *that kidneys swollen with disease are tense, and the inference that relief of this tension by procedures such as decapsulation was feasible.** Second, the observation that a kidney at the height of diuresis is very hard and tense, and the attempt to make the kidney expand still further by clamping the renal vein temporarily, fails Third, the observation[1160, 1161] that in most cases, a rise in the obstructing pressure of the ureter has no effect on urine flow or composition until the rise exceeds a certain value, approximately 10 mm mercury. This is attributed to an intrarenal pressure exerted laterally on some distal part of the tubules, keeping them collapsed until they are forced open by urine which has reached a pressure just greater than that in the renal tissue Beyond this critical value, the curve relating urine flow to ureteral pressure is practically linear and urine flow is abolished by a ureteral pressure of 20 to 30 mm mercury. The main effect here is a reduction of glomerular filtration; a subsidiary one probably being an inhibition of tubular water reabsorption[324]. It can be calculated that the urine flow in the unobstructed kidney would be 50 to 100 per cent higher if the intrarenal pressure could be removed Decapsulation commonly about halves the intrarenal pressure[1166]. Complete *removal of intrarenal pressure is accomplished by inclosing the kidney* in a subatmospheric pressure chamber, whereupon a substantial diuresis occurs which cannot be increased by further lowering of the intrarenal pressure

4 18. *Arterial Blood Pressure and Urine Flow* The minimum arterial pressure which will bring about urine formation in the isolated kidney of the dog at body temperature is 70 to 80 mm mercury (§8 6). Diuretics may lower the minimum pressure consistent with urine formation to about 40 mm mercury, and cooling the blood perfusing the kidney from body temperature to about 3° to 13° C. has the same effect. Cooling changes the composition of the urine substantially to that of a serum transudate, reversible on warming *The chloride concentration, always low at body temperature, is increased by cooling so that below about 18° C it is the same as serum concentration, regardless*

* Although in many cases decapsulation appears to establish an increased urine flow, Culpepper and Findley[260], reviewing the subject of decapsulation for oliguria and anuria, conclude that most evidence indicates that decapsulation has not improved the recovery rate from anuria due to circulatory disturbances or to toxic nephroses They think the main factor in anuria is aberrant tubular function, and that statistics are meaningless where surgeons emphasize only their successes.

CHAPTER V

Body Water Compartments

5 1 It is an adage in physiology that body water is compartmentalized By this is meant not that portions of the total water are rigidly separated each from the other, but that water in the body occupies any of a variety of positions which are volumetrically distinguishable physically, chemically, or mathematically Of many substances that are introduced into the blood stream, a part passes out of the blood vessels and distributes itself in tissue fluids Even in the case of substances which are excreted, wholly or in part, this phenomenon is reversible so that a state of equilibrium can be postulated Under the assumption that equilibrium is maintained while concentrations in these fluids are decreasing during excretion, the volume of body fluid dissolving a substance at the same concentration as the plasma can be calculated Dominguez[305] calls this volume the *volume of distribution* without any implication as to the actual distribution of the substance

VOLUMES OF DISTRIBUTION

5 2 *Some Quantitative Aspects* A fraction of any load of water added to the body is theoretically, and probably actually, capable of finding its way by convection and diffusion into any region already occupied by water Heavy water[539, 793], urea[721], possibly sulfanilamide[834], and other substances seem able to distribute themselves throughout the same regions However, the size of the regions or "spaces"[359] in which substances are dispersed depends upon the nature of the substance (molecular volume, electrical charge, etc) and the state of the organism (water content and distribution, membrane permeabilities, etc)

Volumes of distribution are expressed absolutely in volumetric units such as liters or expressed relatively as per cent of body weight in kilograms (or commonly as cc. per kg) A 70 kg man containing 49 liters of total body water has a volume of distribution of water (or of urea) of 70 per cent of his body weight Deuterium oxide (D_2O) has been found to occupy a volume of distribution of from 63 per cent of the body weight in dogs[405] and man[539] to 73 per cent in rabbits

difficulties which attend the application of this simple theory it is remarkable that the *artificial kidney* has become a reality.* This achievement is due to Kolff[610, 612] who has exhaustively studied this matter and solved many of the basic problems, and to others such as Alwall[31, 32, 33], Murray, Delorme, and Thomas[801], and Skeggs and Leonards[991].

An artificial kidney is now a device which receives blood from an artery of a heparinized man or animal, dialyzes it, and returns it to a vein. Blood may also be circulated from vein to vein by means of a pump Colloid or excess glucose in the bath or exchange fluid (to prevent the formation of edema) may or may not be required, depending on what hydrostatic pressures in the "capillary" (dialyzing tubing) of the artificial kidney are set up in the particular installation.

It is still too early to assess the value of the artificial kidney as a research tool for the study of renal function. Numerous physiological and pathological problems, otherwise apparently refractory, are potentially soluble with it Presumably the artificial kidney will enable investigators to discover physiological significance in the blood levels of numerous substances which do not occur in extremely low plasma concentration normally, and which in disease only rise By establishing equilibria with exchange solutions of specially devised ionic and molecular composition the physiological or pathological behavior of many substances, alone and in combination, can be examined, and in a way *which may distinguish renal and extrarenal phenomena.*

Besides the supplement of an artificial kidney to restore effective physiological regulation in disease, other methods, somewhat less effective, have been used One of these is *peritoneal lavage*[1, 376, 953] with solutions similar to the bath water of an artificial kidney. By *using peritoneal membranes as the instrument of dialysis* a urea clearance approximately half normal can be obtained. This contrasts with the urea clearance of the artificial kidney[610] which may be twice normal Continuous *lavage of the small intestine*[611, 823] is not efficient.

* Transplanted kidneys, except autogenous ones, atrophy.

CHAPTER V

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51. It is an adage in physiology that body water is compartmentalized. By this is meant not that portions of the total water are rigidly separated each from the other, but that water in the body occupies any of a variety of positions which are volumetrically distinguishable physically, chemically, or mathematically. Of many substances that are introduced into the blood stream, a part passes out of the blood vessels and distributes itself in tissue fluids. Even in the case of substances which are excreted, wholly or in part, this phenomenon is reversible so that a state of equilibrium can be postulated. Under the assumption that equilibrium is maintained while concentrations in these fluids are decreasing during excretion, the volume of body fluid dissolving a substance at the same concentration as the plasma can be calculated. Dominguez[305] calls this volume the *volume of distribution* without any implication as to the actual distribution of the substance.

VOLUMES OF DISTRIBUTION

52. *Some Quantitative Aspects.* A fraction of any load of water added to the body is theoretically, and probably actually, capable of finding its way by convection and diffusion into any region already occupied by water. Heavy water[539, 793], urea[721], possibly sulfanilamide[834], and other substances seem able to distribute themselves throughout the same regions. However, the size of the regions or "spaces"[359] in which substances are dispersed depends upon the nature of the substance (molecular volume, electrical charge, etc.) and the state of the organism (water content and distribution, membrane permeabilities, etc.)

Volumes of distribution are expressed absolutely in volumetric units such as liters or expressed relatively as per cent of body weight in kilograms (or commonly as cc. per kg.). A 70 kg man containing 49 liters of total body water has a volume of distribution of water (or of urea) of 70 per cent of his body weight. Deuterium oxide (D_2O) has been found to occupy a volume of distribution of from 63 per cent of the body weight in dogs[405] and man[539] to 73 per cent in rabbits

[793]. The volume of distribution of erythrocytes is essentially synonymous with the volume of the circulatory system and constitutes about 9 per cent of the body weight, the dye T-1824 (Evans blue) is distributed in and rather restricted to the plasma volume (5 per cent of the body weight) although it is found in thoracic and cervical duct lymph [360]. The thiocyanate ion occupies in different species an "available fluid" of 25 to 33 per cent of the body weight [254] which has been identified (not always closely) with the extracellular fluid volume. Sodium and chloride ions [405, 577, 641] have a somewhat similar, largely extracellular distribution The inulin space (extracellular for the most part) is given as 22 per cent of the body weight in dogs and about 16 per cent in man [406].

When a substance not characteristically present in the body is introduced and allowed to distribute itself in all the fluid available to it, it is possible to estimate its load, L, after an appropriate interval if we know the amount introduced and the amount eliminated.* The volume of distribution is then calculated in the symbols previously adopted (see Appendix) as

$$b=\frac{L}{A} \tag{63}$$

If the substance is one which is present in the body before a load is imposed, then

$$b=\frac{L}{(A-A_i)} \tag{64}$$

where A_i is the initial concentration of the substance in the plasma The volume of distribution, as has been shown in §3.23 is also found from the relation

$$b=\frac{C}{\gamma} \tag{65}$$

where in this case, C is the clearance of a no-threshold substance and γ its velocity constant of excretion

Volumes of distribution calculated from the formulas of equations (63) and (64) may have a physical significance different than what is explicit in the computation. Thus, if one attempts to calculate an "extracellular space" from the concentration increment of sodium or chloride after a load of these alone is administered, the volume of distribution obtained will be greater than the extracellular space because

* Substances used to ascertain a volume of distribution should presumably be nontoxic, be rapidly diffusible to attain equal concentration with respect to water in various body fluids, have little effect on hydration of the body, and be neither stored, utilized, nor destroyed by the body in an unpredictable manner.

the osmotic effect of an appreciable load of salt is to draw fluid from the intracellular into the extracellular compartment.* Actually, since it has been established that the concentration of total base throughout the body water is approximately the same and that change in any portion is approximately equalled in all other portions[281, 396, 556, 641, 649, 761, 1149, 1174], the volume of distribution more nearly obtained by using equation (64) for chloride is not that of chloride but that of water.

The reason for this may be gleaned from figure 16. The collective capillary membrane between the extracellular (plasma+interstitial) and intracellular spaces separates compartments whose effective osmotic pressures may be assumed to be identical, although the ions and molecules responsible for the osmotic pressure on each side of the membrane may be different in numbers and types. Salt, introduced and largely confined to the extracellular space, raises the osmotic pressure of that space. Water leaves the intracellular space as a result and the concentration in the latter is raised until it is again in osmotic equilibrium with the extracellular space. It is as if the salt, to judge from its extracellular concentration, were distributed throughout the total body water. The distortion of body volumes in this example consists of an expanded extracellular and a shrunken (dehydrated) intracellular compartment. Hetherington[538] made use of this phenomenon by injecting a limited amount of strong salt solution (8 per cent) into cats and measuring the change in serum osmotic pressure after a steady state was reached. With equation (64) as a basis, she determined the amount of water in the body available to dilute the added salt.

If we assume the following compartmental volumes of distribution in per cent of body weight—plasma, 5 per cent, extracellular fluid, 20 per cent, and total water, 70 per cent—we may approximate the fraction of a load of pure water or of isotonic saline entering certain compartments. Thus, of a load of water, $100\times5/70=7$ per cent swells the plasma volume, $100\times20/70=29$ per cent enters the extracellular space, and $100\times50/70=71$ per cent remains in the intracellular compartment. With isotonic saline these respective augmentations, in per cent of load, would be $100\times5/20=25$ per cent for plasma, $100\times20/20=100$ per cent for extracellular, and 0 per cent for intracellular. These approximations are made on the assumption that the body compartments behave as the chambers of a "perfect osmometer." In the absence of generally recognized corrections for the deviations therefrom, these calculations are instructive and provide a standard of reference with

* Minute loads of radioactive sodium, having little osmotic effect, remove this difficulty[577].

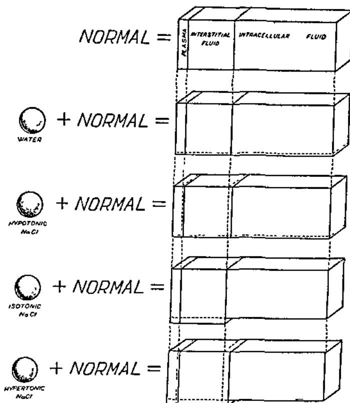


Fig. 16. Diagram Illustrating the Distortion in Body Fluid Compartments which theoretically occurs with positive loads of water or water and salt introduced into the extracellular compartment Broken lines mark the boundaries of normal volume before loading. Solid lines bound final volumes Spheres represent unit volumes of fluid to be loaded

A unit load of water, entering all compartments freely until osmotic equilibrium is established, increases the volume of each compartment in proportion to its initial volume. The effect of hypotonic NaCl solution can be *analyzed into the effect first, of adding some salt alone to the extracellular* (plasma + interstitial) space, giving an osmotic shrinking of the intracellular and expansion of the extracellular space, and second, of adding water which simply adds on to each compartment as before in proportion to its new volume Isotonic saline is confined entirely to the extracellular compartments, adding to these in proportion to their initial volumes The effect of hypertonic saline is conveniently analyzed into the effects of isotonic saline alone plus extra salt added alone to the extracellular space As we go from water to hypertonic saline in the series illustrated, the extracellular space expands more per unit load of fluid and the intracellular space expands less per unit load of fluid, actually contracting with hypertonic loads

which to compare measured volumes under various conditions. In spite of the emphasis laid by some writers on the instances in which the body compartments do not follow simple osmometric changes [illegible], these changes have been repeatedly substantiated by numerous workers including Leaf, [illegible] and [illegible] [illegible], Murphy, Cornell and Grill[illegible], [illegible] and [illegible] [illegible], [illegible] et al. [illegible], and Lyons, Jacobsen, and Avery [illegible]. The latter investigators gave men 20 to 25 grams of sodium bicarbonate or sodium chloride per day for 1 to 2 days under controlled conditions, but with water allowed ad libitum. The carefully measured increments of body weight which they found may therefore be assumed to represent loads of isotonic or slightly hypertonic saline [illegible]. The absolute increments of plasma volume which they report average, with few gross exceptions, close to the theoretically predicted 25 per cent of the saline load.

The author [illegible] has derived an equation defining osmometric relations among volumes of extracellular and intracellular fluid, loads of certain solutes substantially confined to the extracellular space, and loads of water. It is given as

$$V_e' = \frac{(W + L_{H_2O})(V_e A - L)}{W A - L} \qquad [illegible]$$

where V_e and V_e' are the initial and final extracellular fluid volumes in liters (for example, before and after a load of salt with or without water), W is the initial total body water volume in liters, A is the initial concentration in extracellular and in intracellular compartments in osmols per liter (see below, [illegible]), L is the load of solute in the extracellular compartment in osmols, and L_{H_2O} is the load of water in liters. Equation ([illegible]) is that of a "perfect osmometer" and is based on the following assumptions: (1) a load of water, whether positive or negative, is fractionally distributed among plasma, interstitial and intracellular compartments in proportion to their preloaded volumes so that the ratio of increment to initial compartment volume is constant; (2) a load of solute, whether positive or negative, is confined to the extracellular space during the period of equilibration and is distributed between the plasma and interstitial volumes similarly in proportion to their preloaded volumes; (3) the effective osmotic pressure within the intracellular space at equilibrium is equal to the osmotic pressure within the extracellular space [illegible] effective osmotic [illegible] and (4) the quantity of intracellular solute [illegible] equilibration. This latter pressure remains constant for the period of equilibration [illegible] extracellular sodium [illegible] hold even if ionic exchanges (for example [illegible] intracellular potassium) occur.

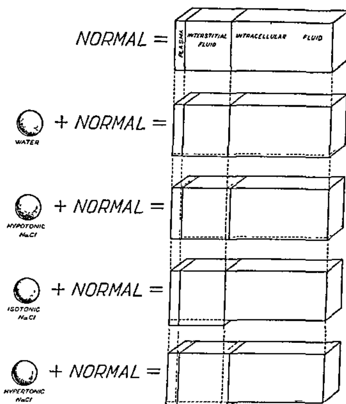


Fig. 16. Diagram Illustrating the Distortion in Body Fluid Compartments which theoretically occurs with positive loads of water or water and salt introduced into the extracellular compartment. Broken lines mark the boundaries of normal volume before loading Solid lines bound final volumes. Spheres represent unit volumes of fluid to be loaded.

A unit load of water, entering all compartments freely until osmotic equilibrium is established, increases the volume of each compartment in proportion to its initial volume. The effect of hypotonic NaCl solution can be analyzed into the effect first, of adding some salt alone to the extracellular (plasma + interstitial) space, giving an osmotic shrinking of the intracellular and expansion of the extracellular space, and second, of adding water which simply adds on to each compartment as before in proportion to its new volume Isotonic saline is confined entirely to the extracellular compartments, adding to these in proportion to their initial volumes The effect of hypertonic saline is conveniently analyzed into the effects of isotonic saline alone plus extra salt added alone to the extracellular space. As we go from water to hypertonic saline in the series illustrated, the extracellular space expands more per unit load of fluid and the intracellular space expands less per unit load of fluid, --tually contracting with hypertonic loads

which to compare measured volumes under various conditions. In spite of the emphasis laid by some workers on the instances in which the body compartments do not follow simple osmometric changes (§6 6), these changes have been importantly substantiated by numerous workers including Lands, Cutting, and Larson[641], Murphy, Correll, and Grill[800], Elkinton and Winkler[337], Winkler et al.[1149], and Lyons, Jacobsen, and Avery[694]. The latter investigators gave men 20 to 25 grams of sodium bicarbonate or sodium chloride per day for 1 to 2 days under controlled conditions, but with water allowed ad libitum. The carefully measured increments of body weight which they found may therefore be assumed to represent loads of isotonic or slightly hypertonic saline (§6 4) The absolute increments of plasma volume which they report average, with few gross exceptions, close to the theoretically predicted 25 per cent of the saline load.

The author[1174] has derived an equation defining osmometric relations among volumes of extracellular and intracellular fluid, loads of certain solutes substantially confined to the extracellular space, and loads of water It is given as

$$V_e' = \frac{(W + L_{H_2O})\,(V_e A + L)}{WA + L} \qquad (66)$$

where V_e and V_e' are the initial and final extracellular fluid volumes in liters (for example, before and after a load of salt, with or without water), W is the initial total body water volume in liters, A is the initial concentration in extracellular and in intracellular compartments in osmols per liter (see below, §6 4), L is the load of solute in the extracellular compartment in osmols, and L_{H_2O} is the load of water in liters. Equation (66) is that of a "perfect osmometer" and is based on the following assumptions (*1*) a load of water, whether positive or negative, is fractionally distributed among plasma, interstitial, and intracellular compartments in proportion to their preloaded volumes so that the [illegible]

w [illegible]

tl [illegible] and is distributed between the plasma and interstitial volumes similarly in proportion to their preloaded volumes; (*3*) the effective osmotic pressure within the intracellular space is equal to the osmotic pressure within the extracellular space at equilibrium; and (*4*) the quantity of intracellular solute exerting effective osmotic pressure remains constant for the period of equilibration. This latter might hold even if ionic exchanges (for example, extracellular sodium for intracellular potassium) occur.

to precipitate circulatory embarrassment in compensated cardiac patien
than is an equal volume of 5 5 per cent glucose solution. But what
the relative effects of equal amounts of salt administered in differe

TABLE VII

Osmotic coefficients and isosmotic concentrations of several substances[659].

Substance	n	Mol Wt.	ϕ	$\frac{\phi n}{\phi_0 n_0}$	Concentration Isosmotic with 160 mM. NaCl	
					mM./kg.	g./kg.
NaCl	2	58 5	0 93	1 00	160	9 36
KCl	2	74 6	0 92	0 99	162	12.1
HCl	2	36.6	0 95	1 02	157	5 74
NH_4Cl	2	53 5	0.92	0 99	162	8 67
$NaHCO_3$	2	84 0	0 96	1 03	155	13 0
$NaNO_3$	2	85 0	0.90	0 97	165	14 0
KSCN	2	97.2	0 91	0.98	163	15.8
KH_2PO_4	2	136.0	0 87	0.94	170	23 1
$CaCl_2$	3	111 0	0 86	1 39	115	12 8
$MgCl_2$	3	95 2	0 89	1.43	112	10 6
Na_2SO_4	3	142 0	0 74	1 19	134	19 0
K_2SO_4	3	174 0	0 74	1 19	134	23.4
$MgSO_4$	2	120 0	0 58	0 62	258	31 1
Glucose	1	180	1 01	0.54	296	53 0
Sucrose	1	342	1 02	0 55	291	99 5
Maltose	1	342	1 01	0 54	296	100 1
Lactose	1	342	1 01	0 54	296	100 1

TABLE VIII

Conversion constants for various units used for osmotic pressure[659]. $T = 310°K$; osmotic coefficient of NaCl taken as 0 93.

	Atm	Mm Hg	Osmolal	Molal NaCl	Δ° C.
1 atm.	1	760	0 0394	0.0212	0 073
1 mm Hg	0 00132	1	$5\ 18 \times 10^{-5}$	$2\ 78 \times 10^{-5}$	$9\ 61 \times 10^{-5}$
1 osmolal	25.4	19300	1	0 538	1 86
1 molal NaCl	47 2	35900	1 86	1	3 46
1° C. Δ	13 7	10400	0 538	0 289	1

strength solutions? Let us compare theoretically the effects of 200 cc of 5 per cent sodium chloride given intravenously with 1000 cc. of 1 per cent sodium chloride. The difference between the increments of extracellular volume (and the roughly proportional plasma volume)

which would result from loads of these solutions is probably too small to be accurately measured by conventional methods for determining these volumes. From the osmometric equation [illegible], however, we may readily estimate (assuming for present purposes that the volume administered is equal to the load retained) the effect of [illegible] grams of salt by each of the above solutions. In Table IX are indicated the absolute and percentual changes in extracellular volumes in 70 kg. men

Table IX

Theoretical effects on extracellular and plasma volumes, and on plasma concentration of sodium, of a load of 10 grams ([illegible] mEq.) of sodium chloride. The salt is given to normally 70 kg. individuals by means of 1000 cc. of 1 per cent NaCl solution L_1, or 200 cc. of 5 per cent NaCl solution L_5. Volumes have been calculated by means of the osmometric equation for conditions with and without an edematous load of 20 kg. of water, and for initially normal plasma concentrations of sodium (A = 140 mEq./L.) and initially hypotonic plasma concentrations of sodium (A = 125 mEq./L.). $A' - A$ represents the increment in plasma concentration of sodium (mEq./L.) effected by loads of solutions L_1 and L_5. V_e and V_e' are the initial and augmented extracellular volumes (liter), respectively, and $100(V_e' - V_e)/V_e$ is the percentual increment sustained by the extracellular volumes.

70 Kg. Subject	A	V_e	$A' - A$		V_e'		$100(V_e' - V_e)/V_e$		
			L_1	L_5	L_1	L_5	L_1	L_5	$L_1 - L_5$
Nonedematous	140.00	14.000	0.520	2.907	15.154	14.522	8.24	[illegible]	[illegible]
Nonedematous	125.00	9.500	0.520	2.968	11.255	[illegible]	[illegible]	[illegible]	[illegible]
Edematous	140.00	34.000	0.483	2.076	35.112	34.779	[illegible]	[illegible]	[illegible]
Edematous	125.00	29.500	0.527	2.119	31.054	30.[illegible]	[illegible]	[illegible]	[illegible]

with or without 20 kg. of edema fluid and with either a normal (140 mEq. of sodium per liter) or hypotonic (125 mEq. of sodium per liter) plasma, initially.* It will be observed from these figures that, if the increment of plasma volume were roughly proportional to the increment of extracellular volume, the added percentual load on the circulatory system caused by the use of 1000 cc. of 1 per cent salt rather than 200 cc. of 5 per cent salt, would be only 1 to 2 per cent.

This percentual difference may be compared with that between the theoretical augmentation of these body compartments by 1000 cc. of

*A concentration of 140 mEq. of sodium per liter, used in the osmometric equation in place of the total effective osmolality, probably represents a slightly hypotonic plasma. [illegible] 150 mEq. per liter is more closely equivalent to the normal osmolality of [illegible]. We do not know what the effective osmotic pressure actually is. Use of lower than normal values in place of normal ones in the osmometric equation results in higher calculated extracellular volumes with given loads of salt.

are exquisitely sensitive to its presence and respond with high rates of excretion per unit load Even if we assume that the pituitary, and not the kidney, directly responds to the water load, the force of our statement concerning renal contact with different salt solutions remains And isotonic sodium sulfate, with much the same volume of distribution as isotonic sodium chloride, behaves more like plain water than like normal saline in its effect on urine flow (§7.18).

It is known that though the kidney does not respond to moderate loads of physiological saline with marked diuresis, it does respond nevertheless with a diuresis which varies in a regular way, depending on the rate of administration And the urinary concentration of sodium and chloride is extremely sensitive to the presence of a load of physiological or any other saline, being modified in such a way as to minimize alterations from the normal plasma concentrations of these ions[1173]. The studies of Merrel, Gellhorn, and Flexner[772] and of Burch, Reaser, and Cronvich[196] indicate the rapidity with which transfers of sodium ion and water are made across capillary-interstitial boundaries With radioactive Na^{24} as a tracer, it was found that 13 per cent of extravascular sodium and 29 per cent of interstitial water are transferred to plasma, per minute. Even in congestive failure the exchange rates are only slowed by a factor of 2. The kidney apparently does not lose contact with interstitial ions and water for long and cannot ordinarily be thought of as isolated.

Kolff's demonstration[610] of the removal of edema fluid into the dialyzing bath of the artificial kidney (§1.16) constitutes another link in the chain of evidence implicating impaired renal function rather than prerenal deviation as a fundamental defect in certain edemas The edema fluid in various interstitia can be considered no more isolated from the artificial than from the natural kidneys, yet the former removes edema where the latter may not.

These experimental observations are not alone in disputing the assumption of sequestered salt depots and renally evasive water.* The sober fact of body volume regulation, practiced in part by the kidney in maintaining normal, undistorted body compartments, implies, a priori, that loads of water and salt are recognized when present and reduced with dispatch. We realize that aberrant and unusual distributions of edema fluid (for example, localized lymphedema) imply the existence of different degrees of renal contact, but the forces acting to distribute fluid and solute loads to the tissues are parts of systems which can come to equilibrium and can act, conversely, to deliver these loads to the

* See also Borst[154] on the untenability of the prerenal deviation concept.

kidneys. The so-called "mobilization" of body fluid by diuretic agents, which has been proved to result in large measure from direct renal action again argues that fluid isolation is not a primary phenomenon but one that depends upon volume regulating mechanisms.

No one will deny an effective prerenal deviation where a tourniquet on the arm substantially isolates the tissues and fluids in this region from direct consideration by the kidney. But this is a reductio ad absurdum So far as the great bulk of body fluids is concerned such disjunction under most physiological and pathological conditions is unknown Even in this case, the kidney will be informed of the new circumstances at least because the residual and smaller volumes of distribution which remain in renal contact will favor new, increased concentration increments per unit load of solute or water Prerenal deviation implies the fallacy which supposes that the nature of physiological activities can necessarily be inferred from observation of certain unphysiological conditions But all of our present considerations contravene the idea that prerenal deviation, per se, constitutes an operating principle in renal physiology

5 5. *Electrolyte Transfers among Body Compartments* Whereas fluid transfers among body compartments give an appearance of simplicity to the extent that they are correlated with one or two experimentally preferred variables, the state of order in the field of electrolyte transfers is less happy Not long ago it was satisfying to categorize certain ions as extracellular, certain ions as intracellular, and others as inhabitants of all body recesses[396] This classification still has scientific value even though it was shown by Heppel[534] and others that exchanges of ions (for example, sodium uptake and potassium loss by muscle cells) occur relatively freely

The kidneys cannot excrete substances which are not brought to within tiny distances of its parenchyma Presumably plasma must be brought to the glomeruli and interstitial fluid to the tubules, and at their respective renal interfaces, gradients are erected which determine the net passage of material into the urine. The regulation of extracellular ionic concentrations thus practiced by the kidney is only a small step from the regulation of intracellular ionic concentrations Exchanges across cell membranes make this possible. How the composition of extracellular fluid can affect the intracellular volume (and thus concentration) is exampled in some work of Hastings and Eichelberger[500] They studied extra- and intracellular phases of muscle in dogs in which an increase in total body water was produced by iso-

tonic salt solutions The *extracellular space was found to increase without* swelling or shrinking of the intracellular space providing the salt solution contained bicarbonate essentially at the normal concentration for extracellular fluid With more or less than the normal bicarbonate concentration increases in the intracellular phase were noted Tarail and Elkinton[1048] have observed that deficits in body potassium in man are frequently but not always associated with abnormally low concentrations of potassium in serum. Yet they find that retention of administered potassium probably indicates a cellular deficit This suggests that the immediate stimulus to renal retention of potassium is not necessarily the concentration of that ion in the extracellular fluid These workers found no clear evidence that the threshold of potassium was elevated (no U/A value less than one was obtained). Serum bicarbonate was elevated in some cases, however, before potassium therapy, and fell to within normal limits after administration of the latter ion (§7 25).

The regulations of the kidney are far-reaching, governing remote *as well as local volumes and concentrations We suspect that the paths* of control are to be found in physical and chemical equilibria and physiological steady states already known, and it is profitable to look for them in these things But there may be other, unknown principles of intercompartmental regulation Certainly there is no assurance that only known physicochemical principles govern the urinary function of the kidney

Fugacity and Renal Function

5 6 *Fugacity in Urinary Flow* In ordinary water balance there exists a pair of equal fugacity gradients (cf. §1.15), one between the gut and the plasma, and the other between the plasma and the kidneys Fluid flows from the enteric region where it has high fugacity to the renal region where it has low fugacity When, for any reason, the renal excretion of water and salt does not keep up with their intakes, these substances flow along lesser fugacious gradients normally existing between the gut and tissue spaces, and edema will result (§1 18, 2 5, 2 6)

The effect of any diuretic agent capable of removing an accumulation of edema fluid, regardless of its specific influence on particular intrarenal processes, is to lower the fugacity of the urinogenic fluid of the kidney with respect to plasma *For example, strongly hypertonic* solutions of glucose behave as diuretic agents and are believed to bring about increased glomerular filtration[961] and to hinder normal tubular

water reabsorption, leading thereby to an increase in urine flow. In the artificial kidney of Kolff[610] glucose added to the dialyzing bath water to form a "hypertonic" solution has the effect of simply increasing "glomerular filtration" (transudation from blood to bath across the cellophane membrane) and accomplishing the same end, namely, the removal of edema fluid In both natural and artificial kidneys the effect of glucose is to lower the fugacity of renal fluid (that is, to make it hypofugic) with respect to plasma, to establish a larger fugacious gradient between intake paths and emunctory, and in this manner to institute increased renal elimination. The relative magnitudes of glomerular filtration and tubular reabsorption are of little consequence There are many possible combinations of glomerular and tubular activities in the normal kidney which can establish particular fugacious gradients, and it is fruitless to seek to enumerate them endlessly.

The action of plasma or colloid transfusions on renal function is another instance in point There is at present no principle in physiology whose rigorous application will enable us to decide what effect an altered oncotic pressure of plasma will have on fluid retention. If it were true (and it is to only a limited extent) that lowered oncotic pressure leads to accumulation of fluid in tissue spaces because of excessive capillary transudation then, for the same reason, glomerular filtration should be increased Whether or not glomerular filtration is actually altered, it is obvious that that factor of itself cannot be responsible for the state of impaired rather than enhanced renal elimination of water and salt which obtains in many instances of lowered plasma oncotic pressure[381, 464]. Conversely, the raising of the oncotic pressure of the plasma as a therapeutic measure, which may be accompanied by the elimination of accumulations of edema, has no rational basis in the filtration process alone There is no need to assume a primary renal action of elevated oncotic pressure but rather an integration of renal and extrarenal actions It is gratuitous, and possibly fallacious, to assume that an elevated oncotic pressure which initiates a flow of fluid from tissues to plasma will hinder the flow from plasma to glomerular capsule in any parallel manner If raising oncotic pressure affects renal function, it probably does so by altering fugacious gradients between compartmental fluids and kidney (§1.18). The particular nephrodynamic responses which occur need not be the same in all cases To think that the details of intrarenal processes, studied alone, will necessarily point the way to all the laws of renal function is delusive.

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supplementary and consecutive processes Passage of water through the mouth produces immediate but only temporary satisfaction of thirst[97]. These facts make it appear that local dryness is consistent with, but unnecessary for the production of the thirst sensation The concept of local dryness as the basis of a theory of thirst does not, alone, sufficiently help to resolve the questions which physiologists ask. The general tissue dryness hypothesis, the osmotic hypothesis, the cellular dehydration hypothesis, or whatever we wish to call the concept which supposes thirst to be of general origin, appears the more useful at the present time even though we do not know precisely the organic receptors for thirst We possess, in any case, a large and coherent body of information on the nature of thirst and its correlative dehydration which does not include a great deal of perturbing data[95]

TABLE X *

State of Body Water Content (Absolute)	Plasma Specific Gravity
Dehydration .	> 1 0290
Normal .	1 0255 to 1 0290
Mild hydration	1.0233 to 1 0255
Edema zone	1 0225 to 1 0233
Edema .	< 1 0225

* After Brown et al [178]

SALT-WATER STATES

6 2 *Absolute and Relative Dehydration, Absolute and Relative Hydration The Conditioned Thirst Reflex* Following the distinction of Adolph[16] between absolute and relative deficits of water, the state known as dehydration should be regarded specifically as one either of absolute or relative dehydration, or some combination of the two By *absolute dehydration* is meant an absolute deficit of water in the body with respect to the normal water content Removal of a liter of water from the body, alone or together with any salts or other materials, creates an absolute deficit of one liter or an absolute dehydration to that extent This condition is known clinically simply as "dehydration" and it is usually characterized by such signs as weight loss, anhydremia, raised plasma specific gravity (Table X) and refractive index[808] (Fig 18), raised concentration of nonprotein nitrogen in

CHAPTER VI

Dehydration and Hydration

6 1 *Dehydration and Thirst* With a few notable exceptions the extent to which an animal is dehydrated is measured by the degree of its manifest thirst. We do not fully know the intrinsic nature of this sensation. Mayer[737], judging from cryoscopic measurements of serum osmotic pressure in dogs during fluid deprivation, believed thirst was tied to the hypertonicity of the milieu intérieur. Cannon[211], however, held that thirst was primarily dependent not on general sensations such as might originate with hypertonic body fluids, but *rather on the degree* of dryness of the mouth, a condition which could well depend on the function of the salivary glands These classic views of thirst, the one holding that the urge to drink water arises locally (dry mouth) and the other holding it to arise generally (dehydrated tissue cells), have been reviewed by Adolph[20]. He concludes that thirst is a many-faceted problem for which no simplified account has proved adequate, and one which requires for solution additional hypotheses and facts Perhaps the "local origin theory" of thirst is merely a special case under the cellular dehydration hypothesis.

It is common experience that the solution formed in the mouth when chocolate candy is chewed, and containing sugar in high concentration, excites thirst so quickly (even though the mouth is wet) that a "general" basis for the sensation would appear to be precluded. Nevertheless it remains true that (*1*) profuse salivary flow does not inhibit the urge to drink[20, 1119] in dehydrated men given pilocarpine to stimulate such flow; (*2*) atropine administration does not significantly increase subsequent water intake[44] nor does total extirpation of salivary glands in dogs increase their average daily water intake[791], (*3*) thirst can be intense during moderate drinking by patients with diabetes *insipidus*, that is, while membranes of the mouth are moist, (*4*) strong solutions of sodium chloride do not relieve thirst regardless of the moistening of mucous membranes; (*5*) forced water drinking (several *liters daily for* several months) can evoke a state of sustained, intense thirst[630, 732, 889]; and (*6*) satisfaction of thirst is not a single process such as wetting the mucous membranes *of the mouth[1175], but a series of at least* two

absolute excess of water in the body with respect to normal water content, the latter is defined by a lowered concentration of the above mentioned extracellular ions Absolute hydration, alone, is characterized by the opposite of those conditions listed above for absolute dehydration, that is, increased body weight, lowered plasma specific gravity (Table X), altered tissue elasticity[927, 949], etc Relative hydration is seen in water intoxication or hyponatremia (§1 3).

Arden[47] observed that when concentrated (10 per cent) solutions of sodium chloride or sodium bicarbonate were taken, thirst developed in about 30 minutes and the secretion of saliva gradually slowed down until after two hours there was no flow Solutions of potassium salt did not lead to thirst In parallel, Gilman[429] noted that voluntary water intake in dogs differed markedly following intravenous injections of hypertonic solutions of sodium chloride or isosmolar urea despite identical increases in the osmotic pressure of the blood After the administration of hypertonic sodium chloride, animals immediately consumed water sufficient to dilute their blood to the pre-injection level whereas after urea less water was consumed and the osmotic pressure of the blood remained elevated The difference in water intake was attributed to the cellular dehydration which resulted from the osmotic effect of sodium chloride, an effect which in turn is due to the relative impermeability of cell membranes to the sodium and chloride ions No similar effect would occur with urea which enters tissue cells relatively freely, exerting little effective osmotic pressure The behavior of potassium, presumably more like urea with respect to cell membranes than sodium or chloride, permits us to place its adipsic or hypodipsic property on the same basis as that of urea

The concept of thirst as a function of cellular dehydration has also been elaborated by others Kerpel-Fronius[598] recognized two forms of experimental water loss, namely, a thirst form of exsiccation due to a disproportion between the excretion of water and other removed substances (relative dehydration), and a salt-loss form which, depending on whether the loss is of sodium or potassium salts, leads to loss of interstitial or intracellular water Remington, Parkins, and Hays[893] partially depleted dogs of extracellular electrolytes by intraperitoneal glucose injections followed shortly by removal of peritoneal fluid When the animals were then maintained on a salt-free diet they showed absence of fluid intake and a negative water balance while the intracellular volumes were above normal. When the intracellular volume returned to normal after several days, water intake began and rose gradually If sodium chloride was given, the initial response was an increased water intake which was not sustained. In general, voluntary intakes showed

plasma, loose, wrinkled skin, soft and receding eyeballs, dry tongue, depressed fontanelle, tendency to acidosis, etc *

By *relative dehydration* is meant a deficit of water relative chiefly to certain extracellular electrolytes, particularly sodium and, less uniformly, chloride. When the concentration of these electrolytes is greater than normal, the state is one of relative dehydration; there may or may

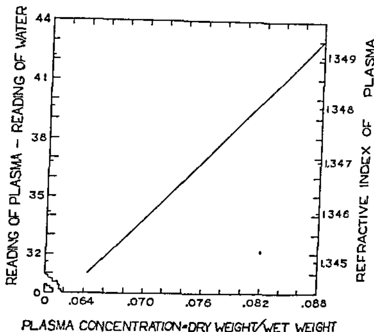


Fig. 18. Refractive Index of Plasma (Right Ordinate) in Relation to Fraction of Solids in Heparinized Plasma of the Dog. Based upon 2 individuals in 21 tests; given water by stomach, or deprived of water with constant diet, or neither The left ordinate is for readings of the dipping refractometer at 17 5° C. After Adolph [16]

not be simultaneous absolute dehydration The cardinal sign of relative dehydration of appreciable degree is thirst[47, 297, 429, 598, 804] which is not an obligatory accompaniment of absolute dehydration[282].

The converses of these respective states of dehydration are termed *absolute hydration* and *relative hydration.* The former is defined as an

* There are categories within the division of absolute dehydration. Painter, Holmes, and Gregersen[835] showed in dogs that rapid dehydration resulting from diuresis with 50 per cent sucrose differs from gradual dehydration following prolonged deprivation of food and water Change in plasma protein concentration constitutes a fair index of reduction in plasma volume in the former instance but not in the latter

to have better opportunity to be locked into conditioned reflex. Where local dryness of the mouth and throat (facilitated by diminished salivary flow, however caused) or osmotic stimulation of their membranes appears to elicit thirst directly, a "conditioned" stimulus may be at work. This conceivably acts through sensory nerves which join a primitive thirst reflex whose primary afferents lie deep in body tissues such as in the central nervous system Strictly, a "thirst reflex" terminates in effectors which cause water to be drunk, but in man, alone, the sensation of thirst provides an index of the excitation of this reflex useful in physiological experimentation

With the idea that thirst arising directly from stimulation of the tissues of the mouth and throat is in the nature of a conditioned rather than a basic thirst reflex, a unified view results which resolves at least temporarily many of the difficulties which have remained refractory to one or the other or both classic views of thirst The rapid induction of thirst from a moist mouth caused, let us say, by eating highly salted anchovies, becomes explicable neither as a "general" tissue dehydration nor as a "local dryness" but rather as a manifestation of a conditioned reflex, where the conditioned stimulus is osmotic activity in the membranes of the mouth and throat and the unconditioned stimulus, which is here dispensed with, is the usually associated parallel dehydration of osmoreceptors The rapid recovery from such thirst without the taking of water, where only small quantities of salt have been so ingested, indicates the "local" nature of the stimulation Conceivably the thirst induced by prolonged, voluntary polyposia also involves some type of conditioning In any case, unification of the classic views of thirst in these terms suggests further experimental tests

6 3 *Nine Salt-Water States* It is possible to combine the main facts of absolute and relative hydration and dehydration, as well as some of their interrelations with renal function, in a single diagram In figure 19 it is readily observed that with absolute and relative scales acting independently there are nine possible *salt-water states* or combinations of absolute and relative hydration and dehydration * Only one of them, represented by Nn, is completely "normal" and only those with the factor d are characterized by thirst † Each of the combinations is clinically or experimentally demonstrable and examples of them are given in Table XI.

* Based on the assumption that the quantity of intracellular solute exerting effective osmotic pressure remains essentially constant (§5 2).

† Where the thirst threshold has been exceeded (§6 4)

more positive correlations with changes in intracellular volume than with changes in extracellular volume[281].

Nadal, Pedersen, and Maddock[804] again described two types of dehydration distinguished by the presence or absence of thirst. One, a simple water deprivation characterized by thirst, oliguria, no circulatory embarrassment, and cured by water; and one, following abnormal salt loss, leading to shrinkage of extracellular and plasma compartments, circulatory disturbance, and not characterized by thirst nor relieved by salt-free liquids, but relieved by sodium chloride solutions. Holmes and Gregersen[553, 554] showed how intravenous injection of 300 cc of 5 per cent sodium chloride in man can cause thirst, stoppage of salivary flow, and a rise in serum chloride. However, ingestion of several hundred cc of water previous to the taking of the salt alleviated the severe thirst and prevented the reduction in salivary flow, but did not prevent the rise in serum chloride which was of the same order of magnitude with or without the ingestion of water These experiments are not incompatible with the idea that thirst is related to cellular dehydration Where water priming was used the cells were presumably hydrated above normal[1174, 1175] initially, with the result that the succeeding salt loading of the extracellular fluid did not have a dehydrating effect on these cells the equal of that where no water priming was used. In any case, in other studies these authors found good correlation between serum electrolyte concentration and thirst Untreated patients with diabetes insipidus had a sodium concentration about 20 mEq/l. higher than those treated with pitressin or those in whom water was forced so as to alleviate thirst Added correlation between these variables is found in studies of adrenal and postpituitary insufficiency[878, 1158, §10 15, 10 17].

We may note here, as well as later (§6 4, 10 10), the conjecture[1175] that the sensation of thirst originates in osmoreceptors of the sort postulated by Klisiecki et al [605] and Verney[1098] to mediate the release of pituitary antidiuretic hormone following elevation of the osmotic pressure of body fluids The dehydration of such receptors would parallel that of general body tissues and the "general" origin of thirst would appear in better perspective as part of a specific "*thirst reflex*" We may suppose that by far the most frequent salt-water state involving thirst under biological conditions is that of the *Dd* type (see Table XI) Where there is sufficient dehydration to stimulate osmoreceptors there is presumably parallel general tissue dehydration, including dehydration of membranes of the oral cavity. Few physiological associations—Cannon[211] cites Schiff who in 1867 suggested "association" as a basis of "dry mouth" thirst—would seem

to have better opportunity to be locked into conditioned reflex. Where local dryness of the mouth and throat (facilitated by diminished salivary flow, however caused) or osmotic stimulation of their membranes appears to elicit thirst directly, a "conditioned" stimulus may be at work. This conceivably acts through sensory nerves which join a primitive thirst reflex whose primary afferents lie deep in body tissues such as in the central nervous system Strictly, a "thirst reflex" terminates in effectors which cause water to be drunk, but in man, alone, the sensation of thirst provides an index of the excitation of this reflex useful in physiological experimentation

With the idea that thirst arising directly from stimulation of the tissues of the mouth and throat is in the nature of a conditioned rather than a basic thirst reflex, a unified view results which resolves at least temporarily many of the difficulties which have remained refractory to one or the other or both classic views of thirst The rapid induction of thirst from a moist mouth caused, let us say, by eating highly salted anchovies, becomes explicable neither as a "general" tissue dehydration nor as a "local dryness" but rather as a manifestation of a conditioned reflex, where the conditioned stimulus is osmotic activity in the membranes of the mouth and throat and the unconditioned stimulus, which is here dispensed with, is the usually associated parallel dehydration of osmoreceptors The rapid recovery from such thirst without the taking of water, where only small quantities of salt have been so ingested, indicates the "local" nature of the stimulation. Conceivably the thirst induced by prolonged, voluntary polyposia also involves some type of conditioning In any case, unification of the classic views of thirst in these terms suggests further experimental tests

6 3 *Nine Salt-Water States* It is possible to combine the main facts of absolute and relative hydration and dehydration, as well as some of their interrelations with renal function, in a single diagram In figure 19 it is readily observed that with absolute and relative water acting independently there are nine possible *salt-water states* or combinations of absolute and relative hydration and dehydration.* Only one of them, represented by Nn, is completely "normal" and only those with the factor d are characterized by thirst † Each of the combinations is clinically or experimentally demonstrable and examples of them are given in Table XI.

* Based on the assumption that the quantity of intracellular solute exerting effective osmotic pressure remains essentially constant (§5 2)

† Where the thirst threshold has been exceeded (§6 4)

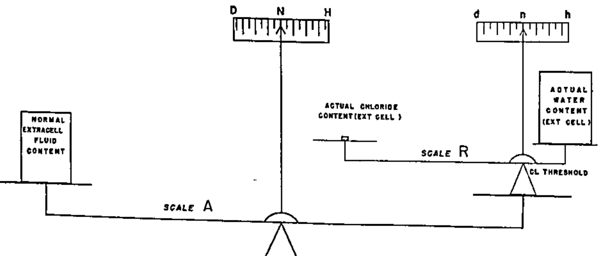


Fig 19. Diagram Illustrating 9 Salt-Water States in Hydration and Dehydration Scale *A* is that of absolute hydration and dehydration Scale *R* is that of relative hydration and dehydration, and the scale *R* itself is assumed to be weightless. When the actual salt (chloride, here) content and the actual water content balance the "normal extracellular fluid content," the absolute water state is normal, *N*. Absolute dehydration, *D*, exists where the actual water content is less than normal, and the indicator points to *H* (absolute hydration) where there is actually more than the normal fluid content present in the body. These absolute states are essentially independent of the relative states of dehydration, *d*, of normalcy, *n*, and of hydration, *h*. When there is a decrease in the actual salt content of the body and no change in actual water content, there is a relative hydration Many combinations of actual salt and actual water content can give states -d, -n, or -h. The diagram aids the visualization of the 9 combinations of absolute and relative hydration and dehydration and the independence of the "absolute" and the "relative" states

The purist may object that adding a weight of salt to scale *R* tips the scale *A* toward *H*. The weight of salt compared with the weight of its solvent must be taken as inappreciable except where it acts through a mechanical advantage greater than can be conveniently (and properly) drawn for scale *R*.

Following this classification we [illegible] or otherwise abnormal conditions [illegible]. [illegible] the three salt–water states [illegible] are

TABLE [illegible]

Salt–Water State	Components	[illegible]
(1) *Hh*	Absolute hydration, relative hydration	After [illegible] of [illegible] hypotonic salt [illegible]
(2) *Hn*	Absolute hydration	After [illegible] of normal saline; generalized edema
(3) *Hd*	Absolute hydration, relative dehydration	After administration of hypertonic [illegible] thirst
(4) *Nh*	Relative hydration	After drinking water [illegible] sive water and salt [illegible]
(5) *Nn*	Normal water content and normal electrolyte concentration	During normal [illegible]
(6) *Nd*	Relative dehydration	After administration of [illegible] out water; after [illegible] without water
(7) *Dh*	Absolute dehydration, relative hydration	After severe [illegible] following which [illegible] weight is [illegible] Incipient water [illegible]
(8) *Dn*	Absolute dehydration	After proportional [illegible] as in fresh [illegible] removal of [illegible] amounts
(9) *Dd*	Absolute dehydration, relative dehydration	After [illegible] or without [illegible] loss with [illegible] most common [illegible] as "dehydration" [illegible]

types found in water intoxication or hypochl[illegible] We can denote five types of dehydration [illegible] salt–water [illegible] again [illegible]

Hn, *Hd*); etc

It is interesting to consider the thirst which may follow hemorrhage. With the decreased plasma and extracellular volume consequent to the loss of blood, it would appear that any further loss of a unit volume of water from the body would result in a greater concentration of the remaining sodium in its smaller volume of distribution than normally. In addition to this diathesis there is the fact found by Borst[154] that posthemorrhagically there may be a cessation of chloride excretion, which would favor the increased concentration of osmotically active ions in extracellular fluids and promote cellular dehydration At the same time increased excretion of potassium[1033] further favors loss of cell water With the tendency of both of these metabolic changes to promote restoration of plasma volume there tends also to result a cellular dehydration and thirst, slaking of which contributes still further to the restoration of normal volumes of body compartments It is not unlikely that hemorrhage raises the chloride threshold

It will be observed that the location of the fulcrum of the relative scale in figure 19 has a unique significance in that the distance at which it must be placed from the water and from the salt pans to balance scale *R* at *n* measures the threshold of retention (§7.2) for either chloride or sodium, whichever may be under consideration If weights of salt and water are *S* and *W* and the respective distances of their pans from the fulcrum are *s* and *w*, then $Ss=Ww$; and $w/s=S/W$=normal plasma concentration=threshold of retention No-threshold substances are not required (and would not be placed) upon the left-hand pan of scale *R* in order to balance the actual water content of the extracellular fluid The fulcrum would be directly under the right-hand pan, and the threshold of retention would be zero There is no physiological interdependence of solute and water With regard to chloride or sodium and water, it could be said that certain cortical hormones, raising the threshold of the former, tend to move the fulcrum of scale *R* to the left while mercurial diuretics, lowering the threshold, tend to move the fulcrum to the right No suggestion is intended through figure 19 that cellular dehydration and thirst are dependent on the renal threshold Thus, if the fulcrum moved to the right, the reading *-d* would not indicate thirst. If thirst varies with the absolute degree of cellular dehydration[1175] the use of figure 19 is apropos only where normal renal thresholds obtain.

The use of absolute and relative scales serves to illuminate the physiology of salt–water states These states are compound balances of water and salt controlled by both intake, where thirst is a prime regulator, and by emunctory, where renal function is dominant; and important degrees of regulation are effected by hormonal control What is still unclear is the mechanism which regulates the size of the "normal extracellular fluid volume."

McCance[740] found that removing 25 to 30 per cent of the body extracellular ions (forced deficit of sodium and chloride through low salt intake and sweating) without limiting water intake resulted in aberrations of flavor sense, cramps, weakness, lassitude, severe cardio-respiratory distress on exertion, negative nitrogen balance,* and high blood urea. Additional symptoms of *hyposalemia* encountered clinically and which may generally characterize a condition of low osmotic pressure of body fluids, include anorexia, nausea, low pulse pressure (volume), increase in pulse rate, clammy skin, drowsiness, apathy, mental onfusion, dehydration, and coma. Loss of flavor has been thought be characteristic of hyposalemia[740] and is "sometimes mistaken or thirst" but is not relieved by plain water[1018]. It is relieved by taking sodium chloride which may then lead to "real" thirst.

Soloff and Zatuchni[1018] and Schroeder[946] have described a syndrome of salt depletion induced by a regimen of sodium restriction for the purpose of favoring the removal of edema fluid in man. It is apparently the clinical counterpart of experimental salt deficiency and includes oliguria. Symptoms are aggravated by the lyuretic effects of mercurial diuretics and relieved by the administration of salt. In rabbits, extreme loss of chloride on a salt-poor diet coupled with xanthine administration leads to hyperreflexia, paralysis, and death[470].

Possibly the significant and symptomatic differences between wate intoxication (§1.3) and low salt syndrome or experimental salt deficiency reflect, respectively, different aspects of acute and chronic hyposalemia.

6.4 *Osmometric Analysis of Thirst.* The cellular dehydration ypothesis of thirst has recently been studied[1175] using as a tool e osmometric equation (66) of §5.2 and the Osmometric Thirst Diagram (Fig. 20). By infusing hypertonic solutions of sodium chloride into dogs and men, loads of salt and water which just provoke thirst can be established. From these data, theoretically, the relative cellular lehydration required to initiate thirst (τ) can then be computed. In an this cellular dehydration constituting the thirst threshold is found average no more than 1.23 per cent (100τ). This calculated, critical ficit in cellular water content (essentially equal to the calculated rement in osmotic pressure of body fluids at large) is similar in nitude and related in significance to the osmotic threshold of

* ought to result from increased protein catabolism following increased adreno-l activity in response to salt deficit[651].

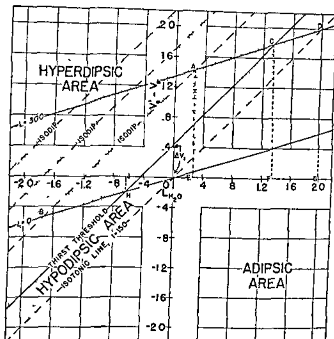


Fig 20 Osmometric Thirst Diagram based on a 70 kg. man containing 49 liters of total body water and 14 liters of extracellular fluid. Ordinate: change in extracellular volume in liters $(V_e'-V_e)$. Abscissa: load of water in liters (L_{H_2O}). The retention concentration lines $(I=L/L_{H_2O}$, of figure 17) and most of the salt load lines (L) have been omitted for clarity. The thirst threshold, separating the hyperdipsic area (densely stippled) from the hypodipsic area (sparsely stippled) is the heavy line, parallel to the isotonic line, which intersects the ordinate at ΔV_i. The value for ΔV_i was obtained by using the average r value found in human experiments (0 0123). Thus, where the cellular water in a 70 kg man is taken as 35 liters, $\Delta V_i = 0\ 0123 \times 35\ 000 =$ 0 431 liters

An isodip is a line (for example, AB) which is the locus of all points (L_{Na}, L_{H_2O}) of equal thirst. For a hyperdipsic point, A, one measures the degree of thirst by passing a salt load line (in this case, $L = 300$) from A to the thirst threshold at C or to the isotonic line at D. The projections EF and EG measure, respectively, the volume of water required to move from the given hyperdipsia to hypodipsia, and from the given hyperdipsia to adipsia. Quantities of water required to relieve hyperdipsia may be determined directly from the equations of thirst

From the intersection of the thirst threshold and the salt load line, $L = 0$, at H, the perpendicular to J may be erected. The abscissal distance from J to the origin represents the absolute water deficit, with no salt loss, which should just provoke thirst, according to the cellular dehydration hypothesis. The value shown here, namely, —0 60 liters, represents a deficit of 0.86 per cent of the body weight. Algebraically, this latter value is equal to $70r$ (total body water as per cent of body weight, multiplied by 0 0123). After Wolf [1175].

Verney's osmoreceptors (§§ 37, 10 10) supposed to lie on the afferent side of a "water conservation" reflex in which the posterior pituitary is an effector. It is suggested that the same or closely related osmoreceptors may be part of a "thirst reflex."

The objective quantification of thirst has required the introduction of certain new words (Fig 20) *Hyperdipsia* is the term used to denote sensible thirst which is relatively temporary, as opposed to "polydipsia" which is relatively sustained *Hypodipsia* denotes an insensible or twilight thirst. It is a condition of hypertonicity of body fluids insufficient to initiate drinking but sufficient to sustain drinking once initiated

More suitable in general than the graphic method of determining the quantity of water (Q_τ) required to bring a hyperdipsic individual to the thirst threshold, or the quantity of water (Q_N) required to restore his body fluids from dipsogenic hypertonicity to isotonicity, is the use of what have been called the equations of thirst These are

$$Q_N = \frac{L}{A} - L_{H_2O} \tag{70}$$

and

$$Q_\tau = \frac{(1-\tau)(WA+L)}{A} - (W+L_{H_2O}) \tag{71}$$

where A is the effective osmolal concentration of isotonic extracellular fluid which may be equivalently approximated by a value of 150 mEq/l of sodium, L is the load of solute substantially confined to the extracellular space (in the case of sodium chloride this load could be expressed in mEq), L_{H_2O} is the load of water in liters, and W and τ are as previously described (see Appendix) Equations of thirst are derived as follows consider a hyperdipsic state where effective osmotic concentration of body fluids is A' If the total quantity of salt in the body remains unchanged after drinking water in amount sufficient to restore isotonicity, A,

$$A(W+L_{H_2O}+Q_N) = A'(W+L_{H_2O}) \tag{72}$$

Also,

$$A' = \frac{WA+L}{W+L_{H_2O}} \tag{73}$$

Substitute (73) in (72)

$$A(W+L_{H_2O}+Q_N) = WA+L \tag{74}$$

$$AQ_N = WA+L-(W+L_{H_2O})A \tag{75}$$

olving for Q_N we obtain equation (70) directly. By substituting /(1−τ) for A in equation (72), we derive equation (71) by steps paralling (72) to (75).

An *isodip* is a line on the osmometric thirst diagram (Fig. 20) which the locus of all points of equal thirst. This is so in the objective sen that equal quantities of water are required to bring an individual fro these hyperdipsic points to isotonicity (isodip of the Q_N type), or small

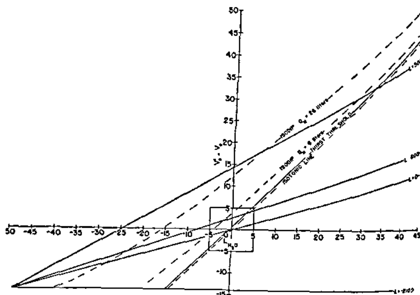


Fig. 21. An Extended Osmometric Thirst Diagram illustrating, in fuller perspective than figure 20, theoretical aspects of isodips and salt load lines The small, central square containing the stippled hyperdipsic area, corresponds to an entire Osmometric Thirst Diagram, including isotonic line and thirst threshold. These lines as well as salt load lines ($L = -2100$, 0, 600, and 5000 mEq of sodium) and two isodips ($Q_N = 6$ and 26 liters) are drawn far beyond physiological limits. It may be observed how salt load lines, while convergent to the point, $V_e - V_s = -V_e$, appear nearly parallel in the limited physiological graph. Also, an isodip (Q_N), whose physiological segment appears to be a straight line, is actually curved and asymptotic with the isotonic line.

but equal quantities of water are required to bring an individual from these hyperdipsic points to the thirst threshold (isodip of the Q_T type). From the equation of thirst (70)

$$L = A(Q_N + L_{H_2O}) \tag{76}$$

Replacing L in the osmometric equation (66) by its value in (76) and subtracting V_e from both sides of the resulting equation we obtain

$$V_e' - V_e = \frac{(W + L_{H_2O})\,(V_e + L_{H_2O} + Q_N)}{W + L_{H_2O} + Q_N} - V_e \tag{77}$$

Equation (77) is the equation of an isodip of the Q_N type (Fig. 21). Similarly derived, using equation of thirst (71) the equation of an isodip of the Q_r type is

$$V'_e - V_e = \frac{(W + L_{H_2O})\,(V_e + L_{H_2O} + Q_r + W_T}{W + L_{H_2O} + Q_r + W_T)} - V_e \quad (78)$$

Figure 22 combines the elements of figures 17 and 19 in depicting the quadrature of salt-water states on the osmometric diagram

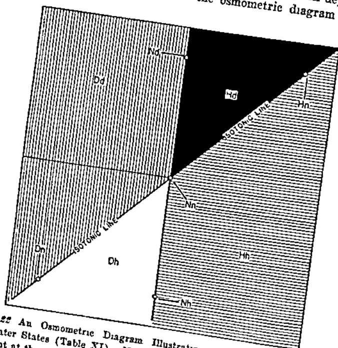


Fig 22 An Osmometric Diagram Illustrating the Location of the 9 Salt–Water States (Table XI) Normalcy, both absolute and relative (*Nn*), is a point at the origin having no dimensional extension States *Nd* (ordinate above origin), *Nh* (ordinate below origin), *Hn* (isotonic line, 1st quadrant), and *Dn* (isotonic line, 3rd quadrant) are abnormal in one respect, either absolute or relative, and are represented in one dimension States *Hd*, *Hh*, *Dh*, and *Dd* are abnormal in two aspects, absolute and relative, and are represented in two dimensions (by areas) Ordinate and abscissa as in figure 20

65. *The Dehydrating Action of Administered Water* An early study by Adolph[9] revealed that ingestion of water alone does not compensate the normal loss of urine, that is, it has no absolutely hydrating action[381]. However, dehydration, per se, does not necessarily

An *isodip* is a line on the osmometric thirst diagram (Fig. 20) which is the locus of all points of equal thirst. This is so in the objective sense that equal quantities of water are required to bring an individual from these hyperdipsic points to isotonicity (isodip of the Q_N type), or smaller

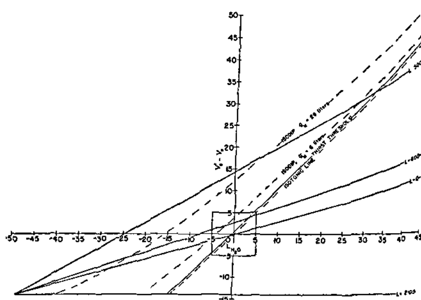


Fig. 21 An Extended Osmometric Thirst Diagram illustrating, in fuller perspective than figure 20, theoretical aspects of isodips and salt load lines The small, central square containing the stippled hyperdipsic area, corresponds to an entire Osmometric Thirst Diagram, including isotonic line and thirst threshold. These lines as well as salt load lines ($L = -2100$, 0, 600, and 5000 mEq. of sodium) and two isodips ($Q_N = 6$ and 26 liters) are drawn far beyond physiological limits It may be observed how salt load lines, while convergent to the point, $V_e - V_e = -V_e$, appear nearly parallel in the limited physiological graph. Also, an isodip (Q_N), whose physiological segment appears to be a straight line, is actually curved and asymptotic with the isotonic line

but equal quantities of water are required to bring an individual from these hyperdipsic points to the thirst threshold (isodip of the Q_T type). From the equation of thirst (70)

$$L = A(Q_N + L_{H_2O}) \tag{76}$$

Replacing L in the osmometric equation (66) by its value in (76) and subtracting V_e from both sides of the resulting equation we obtain

$$V_e' - V_e = \frac{(W + L_{H_2O})\,(V_e + L_{H_2O} + Q_N)}{W + L_{H_2O} + Q_N} - V_e \tag{77}$$

and other symbols are as before (see also Appendix) Solving for u/i we get

$$\frac{u}{i}=\frac{A_T}{A_T-U_{Cl}}=\frac{100}{100-U_{Cl}} \tag{80}$$

Equation (80) shows that the ratio of the urine flow to the intake rate is greater than unity so long as there is a "leakage" of salt into the urine. Were no salt lost into the urine, or from the body, a balance between intake and output of water could be struck Since there is normally a steady leakage of salt (of the order of 20 mEq per liter of urine in the first several hours of water intake), the total fluid output should theoretically be 25 per cent greater than the intake in order to prevent the plasma from being diluted. Thus, 100/(100—20)=1 25 so that $u=1\ 25i$ Indeed, when corrected for insensible water loss* actual urine flows agree well with calculated values, indicating that in renal excretion the regulation of concentration of plasma chloride takes precedence over the regulation of body volume under these conditions (Table XII) This principle has been affirmed by others[395, 1035, 1173] although McCance[740] has shown that in certain cases of forced loss of sodium and chloride the human body seems to compromise between the maintenance of total osmotic pressure and the maintenance of plasma and extracellular volume. In initial stages of salt loss, water

TABLE XII

The theoretical u/i ratios which obtain for given "leakage" concentrations of chloride, U_{Cl}, if normal plasma concentration of chloride is maintained Calculated from equation (80) (§ 6 5), for $A_T=100$ mEq of chloride per liter.

U_{Cl} (mEq /l)	$\frac{u}{i}$
0	1 00
20	1 25
40	1 67
60	2 50
80	5 00
100	infinity

* To correct for insensible loss of water, w, relate the excretion rate of chloride to $(u+w-i)$ cc /min and obtain

$$\frac{u}{i}=\frac{A_T(1-\frac{w}{i})}{A_T-U_{Cl}} \tag{81}$$

cause depletion of salts[125] and other constituents and in these instances water will restore body volume. In effect these observations show that water administration will undo states of relative dehydration but it has no significant effect, except temporarily, in producing absolute hydration[232]. Gamble[395, 398] has substantiated this principle particularly in his treatment of the difference between the retention of saline and of plain glucose solutions in the extracellular fluid It is now generally recognized that there is a difference so far as the water and salt balance of the body is concerned whether one takes water alone or water with a variable quantity of salt.

The author[1171] has investigated quantitatively the effect of continuously administered water on the water balance in man If one drinks plain water at a constant rate (for seven hours) his urine flow after about two hours takes on a rate in excess of the rate of water intake, that is, there is a steady, absolutely dehydrating action of continuously administered water. This is also the case when 5 per cent aqueous solutions of glucose are taken intravenously for long periods at steady rates[1173]. Actual urine flow depends also upon the rate of fluid deflection into extrarenal channels of loss. The theory of this steady state follows

A liter of water loaded on a man makes his water load positive. When the liter is excreted and he regains his original water content, his salt load is negative due to the urinary loss of salt colligated with water If the kidneys are to keep the plasma concentration essentially constant (which they do), one method of succeeding would be to excrete additional water and reconcentrate the diluted plasma[401, 403, 404, 1173] Even the removal into the urine of salt solution, provided it be more dilute than the plasma, would accomplish this end It is hypothesized that during a steady state of water intake the excess of water loss above intake should be related to the quantity of salt lost. In a steady state the rate of excretion of salt per excess of fluid output over intake should be equal to the normal plasma concentration of, let us say, chloride (that is, equal to the threshold of retention) since only by removing from plasma a solution of concentration equal to that of the plasma itself can that plasma be left with the same concentration, that is, at its threshold of retention with respect to chloride (§7 2). The same should be true for sodium Let us state

$$\frac{uU_{Cl}}{u-i}=A_T \qquad (79)$$

where A_T is the normal plasma concentration of chloride (mEq/l) or threshold of retention, i is the rate of intake of fluid (cc/min.),

by a type of "osmotic" intracellular water loss simultaneously which may be largely independent of osmotic loss brought about by increased concentrations of substances confined to the extracellular space. Elkinton and Taffel[335] state that in dogs deprived of food and water for 11 to 20 days, intracellular water loss occurred in three phases, loss on an osmotic basis (increased concentration of substances in the extracellular space), loss associated with cell destruction in fasting, and loss associated with removal of potassium in excess of nitrogen*

Actually the total concentration of electrolyte within cells does not closely indicate the effective osmotic pressure which will be exercised

TABLE XIII

Mineral distribution in skeletal muscle of the dog Average figures based on data in the literature. Values are expressed on the basis of 1 kg. of fat-free muscle Extracellular water content equals 990 g per kg of extracellular phase Intracellular water content equals 717 g per kg of intracellular phase[798]

Constituent	Extracellular Water mEq /kg	Intracellular Water mEq /kg
Total base	156 6	195 6
Na	146 3	12 0
K	3 8	137.4
Ca	3 2	3 2
Mg	1 3	38 5
Cl	129 4	none
P	2.6	117 3

by the cell contents It is well known, for example, that some of the intracellular potassium is osmotically inactive, indiffusible, or "bound" [338, 1037, 1182], a fact which has been used to account for the failure of a cell to behave as a perfect osmometer[339] However, as Bayliss[90] has stated, osmotic pressure is shown only by *free* electrolytes In estimating the osmotic pressure due to the potassium salts in a cell, that part of the salts adsorbed on surfaces must be left out of account. Although the concentration of potassium may be greater at the cell boundary, it does not follow that its osmotic pressure is any greater there, because it is concentrated on account of its property of lowering surface energy, and to do this it must be held in constraint by the

* The normal ratio of potassium to nitrogen in dog muscle is given as 2 38 mEq potassium per gram of nitrogen[500]

and salt are apparently lost in proportion as indicated by the steady state equations above, but further salt loss results in some lowering of the plasma concentrations of sodium and chloride. It has been shown repeatedly[334, 335, 763, 1174] that in depletion of sodium, chloride and water the primary loss is that of fluid from the plasma and interstitial compartments, almost in proportion to their initial volumes

Stewart and Rourke[1035] have compared the effects of continuous infusions in man to the extent of several liters daily of plain glucose and of normal saline They showed that 5 per cent glucose solution caused a dehydration referable to salt loss via the kidney whereas no net loss, but rather a temporary increase in body water, was produced by saline. The force of these observations is that water alone, while it may relieve a relative dehydration, cannot relieve absolute dehydration In the presence of normal renal function physiological saline (0.85 per cent) will relieve both absolute and relative dehydration although it appears that saline solutions more dilute than physiological, that is, about 0 4 per cent sodium chloride, may be better clinically for relieving salt–water states of the *Dd* type[716, 1172] (§7 10).

6 6. *Intracellular Water Loss* The salt–water types so far noted do not concern changes in intracellular electrolytes and constitute only one facet of salt–water balance Important salt–water imbalances are found in which the intracellular content of electrolytes is altered

In water deprivation, or upon the injection of hypertonic solutions of sodium chloride or other salt, an increased excretion of potassium in the urine occurs[335, 337, 598, 1141, 1173, 1177]. Hypertonic solutions of sodium sulfate bring on calcium and magnesium lyuresis but no increased excretion of sodium above that electroneutralized by sulfate[950, 952, 1177]. It appears that potassium excretion is greater when normal saline is given than when plain glucose in water is given[1035] as if there were a graded series of influences upon potassium excretion in proportion to the osmotic pressure of body fluids. The osmotic pressure of the plasma apparently affects the rate of excretion of sodium and other ions as well[461, 952, 1170]. The distortion factor in excretion (§2 4) may underlie this phenomenon, operating in a mechanism of osmotic homeostasis However, Elkinton and Winkler [337] state that hypertonicity is a favorable but not essential condition for this response, and Holmes[552] finds little loss of potassium in dehydration following administration of 50 per cent sucrose. Loss of potassium in large quantities reflects intracellular loss since the extracellular content of potassium is so low. Such loss is accompanied

by a type of "osmotic" intracellular water loss simultaneously which may be largely independent of osmotic loss brought about by increased concentrations of substances confined to the extracellular space. Elkinton and Taffel[335] state that in dogs deprived of food and water for 11 to 20 days, intracellular water loss occurred in three phases; loss on an osmotic basis (increased concentration of substances in the extracellular space), loss associated with cell destruction in fasting, and loss associated with removal of potassium in excess of nitrogen.*

Actually the total concentration of electrolyte within cells does not closely indicate the effective osmotic pressure which will be exercised by the cell contents. It is well known, for example, that some of the intracellular potassium is osmotically inactive, indiffusible, or "bound" [338, 1037, 1182], a fact which has been used to account for the failure of a cell to behave as a perfect osmometer[339]. However, as Bayliss[90] has stated, osmotic pressure is shown only by *free* electrolytes. In estimating the osmotic pressure due to the potassium salts in a cell, that part of the salts adsorbed on surfaces must be left out of account. Although the concentration of potassium may be greater at the cell boundary, it does not follow that its osmotic pressure is any greater there, because it is concentrated on account of its property of lowering surface energy, and to do this it must be held in constraint by the

TABLE XIII

Mineral distribution in skeletal muscle of the dog. Average figures based on data in the literature. Values are expressed on the basis of 1 kg. of fat free muscle. Extracellular water content equals 990 g. per kg. of extracellular phase. Intracellular water content equals 717 g. per kg. of intracellular phase[798].

Constituent	Extracellular Water mEq/kg	Intracellular Water mEq/kg
Total base	156.6	195.6
Na	146.3	12.0
K	3.8	137.4
Ca	3.2	3.2
Mg	1.3	38.5
Cl	129.4	none
P	2.6	117.3

* The normal ratio of potassium to nitrogen in dog muscle is given as 2.38 mEq potassium per gram of nitrogen[500].

surface, adsorbed in fact, and thus unable to possess the kinetic energy necessary for the manifestation of osmotic activity.

The recognition of the role of potassium in certain types of cellular dehydration has led to therapeutic applications, notably by Darrow[279, 455], who finds that potassium administration is essential for recovery from dehydrations involving potassium depletion, as in diarrhea in infants When potassium leaves cells it may be replaced by sodium with a resulting tendency toward acidosis, and the reverse occurs when intracellular sodium enters extracellular fluid[277]. Renal function acting on the modified ionic content of the extracellular fluid brought about by unusual exchanges across cell membranes conceivably conditions these exchanges. At the present time it is difficult to evaluate these remote urinary functions of the kidney in terms of the body economy

CHAPTER VII

Renal Regulations

7 1. It is in the province of renal physiology that one determines the blood flow of the kidney, its oxygen consumption, or the tubular reabsorption of glucose It is more specifically in the province of urinary physiology that one determines the excretory colligations of sodium, potassium, chloride, and other ions, and water; and of urea and other nonelectrolytes The essence of the urinary function of the kidney lies in those laws, known and to be discovered, which describe the interrelations of these substances With sufficient knowledge it should be possible to infer the relative retentions and excretions which will occur when these substances exist in the body in varying states of surfeit or paucity

Much of the work on the excretion of solutes and water has been performed with limited objectives in view. Thus, diverse experimental conditions and techniques have been employed and the results obtained are frequently unsuitable for integration into, or analysis by, hypotheses of broader scope. The clearance technique, applied in recent years to the study of renal excretion, has provided uniformity of procedure but the results for urinary physiology, with some exceptions, have been disappointing While suited to the analysis of nephrodynamics, that is, the dissociation and definition of glomerular, tubular, and vascular functions, the clearance is not the best tool for establishing interrelations among excretory rates of different solutes and water The numerous determinations of tubular reabsorption or secretion which have been made in its name have contributed little to fundamental knowledge which was unknown prior to the elaboration of the clearance concept These determinations have simply filled the gaps in a proposed system of renal function whose reference point is a particular physiological doctrine, namely, that the clearance of inulin is numerically equal to the glomerular filtration rate under experimental conditions of interest This monograph is not concerned primarily with renal dynamics, the vast literature of which is treated elsewhere, but rather with the gross urinary function of the kidney expressed in the regulation of body concentrations and volumes Consequently the discussion of these subjects is differently based than on the surmise that one can at any time

ascertain the glomerular filtration rate If both bases (or others which may be employed in future investigations) are sound, the results of the two approaches should ultimately be found complementary.

Renal Thresholds

7 2. *Thresholds of Excretion (Appearance) and Retention* The concept of the renal threshold is attributed to Bernard[106] and to Gottlieb and Magnus[447] who believed that some kinds of renal excretion, for

Table XIV

Thresholds of excretion (or appearance) of some molecular and ionic substances, expressed as plasma concentrations.

Substance	Threshold of Excretion	Species	Source of Data
Plasma protein	9 6 to 10 4%	Dog	Terry et al.[1051]
Hemoglobin	0 1%	Dog	Monke and Yule[790]
Chloride	85 mEq/l	Rabbit	MacKay and MacKay[696]
Bicarbonate	25 mEq/l.	Dog	Pitts and Lotspeich[865]
Glucose	11 6 mM/l. (0 21%)	Dog	Shannon and Fisher[967]
Glucose	7 8 to 11 1 mM./l. (0 14 to 0.20%)	Man	Peters and Van Slyke[844]
Calcium	4 25 mEq/l.	Man	Albright and Ellsworth[27]
Sulfate	2 to 4. mEq/l.	Dog	Lotspeich[688]
Potassium*	2 8 mEq/l.	Man	Griffon[468]
Phosphate	1.1 to 1.5 mM./l	Dog	Pitts[861]
Uric acid	0.267 mM/l. (0.0045%)	Man	Brøchner Mortensen[173]
Ascorbic acid	0 1 mM/l (0.00176%)	Man	Ralli et al [880]; Smith[1002]
Iron	0.1 mEq/l (0.0002%)	Man	Vannotti[1085]

* Calculated from the ureosecretory constant of Ambard[34, 35, 40]. The fallaciousness of the Ambard formula has been treated by De Wesselow[290].

example, that of glucose in the urine, depended upon whether the plasma level of a certain constituent exceeded a critical value called the threshold concentration Ambard[36, 40] and Cushny[268] have contributed to the definition of a renal *threshold of excretion* which can be stated to be that plasma concentration of a substance above which the substance appears frankly in the urine, and below which it does not appear in the urine in appreciable quantities (Table XIV). The apparent simplicity of this idea of renal threshold has led to its wide adoption Some have used it to accumulate specific data on threshold values[488, 865, 1008], to demonstrate the usefulness of clearance analysis to the inte-

gration of older and newer renal concepts[999, 1002], or actually to deny the existence of thresholds[488] and recommend that the concept be abandoned[24]

Clearance analysis applied to the threshold of excretion or *threshold of appearance,* as it has been called[298, 1171], reveals that it is not a critical concentration but rather, as in the case of glucose, a range of concentration In the lower parts of this range the reabsorptive capacity of certain tubules may become saturated before that of others, resulting in the "spilling" of glucose in the urine Since the difference between the rate of loading of the tubules with glucose from the glomeruli and the actual rate of excretion of glucose by the kidney is considered the rate of reabsorption by the tubules, a maximal rate of reabsorptive transfer of glucose by the tubules (that is, the *Tm*) is correlated with the threshold concentration The modern view dissociates the threshold of appearance from strict relation to plasma concentration because of variations in filtration rate, that is, this threshold may depend on the glomerular filtration rate Yet it recognizes none the less that plasma concentration of a substance is often a most convenient indicator of the probable degree of its urinary excretion Where there is no clearly ascertainable *Tm*, as for chloride[488], the absence of that *Tm* has been correlated with the absence of a threshold This is equated to the fact that at widely varying plasma levels, chloride may be found in the urine However, since chloride does practically disappear at very low plasma levels and when circulatory function is sufficiently upset, it may in this sense be said to have a threshold of excretion

There is another concept of threshold concentration with a physiological significance different from that of the threshold of excretion or appearance It has been elaborated by Rehberg[890, 891], Conway and Kane[239], Dillon[298, 299, 300], Peters[841], and Wolf[1170-1173, 1176, 1177] and is exemplified not by the "point of extinction" or plasma concentration below which substances no longer appear in the urine, but by the point at which concentrations of a given substance in the urine and in the plasma are identical[836, 841] This latter "point" or concentration has been called the *threshold of retention* [1171] and for some substances such as chloride and sodium this threshold concentration is probably synonymous with the normal plasma concentration and is relatively independent of the glomerular filtration rate The threshold of retention is not always the same as a "normal" plasma concentration. Potassium and sulfate are usually at plasma concentrations in excess of their thresholds while glucose and bicarbonate are usually below their thresholds

If the plasma concentration of a substance like sodium falls below its threshold of retention the urine formed, regardless of its volume,

ascertain the glomerular filtration rate. If both bases (or others which may be employed in future investigations) are sound, the results of the two approaches should ultimately be found complementary.

RENAL THRESHOLDS

7.2 *Thresholds of Excretion (Appearance) and Retention* The concept of the renal threshold is attributed to Bernard[106] and to Gottlieb and Magnus[447] who believed that some kinds of renal excretion, for

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Glucose	11.6 mM./l (0 21%)	Dog	Shannon and Fisher[967]
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Uric acid	0 267 mM /l. (0 0045%)	Man	Brøchner-Mortensen[173]
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The constancy of the threshold of retention as compared with that of the threshold of appearance has nothing to do with the preference which has been given the former by some investigators, as has been declared [862]. Indeed, it must be acknowledged that both thresholds are variable[66, 1172]. It should be noted that a substance with a threshold of excretion may have no clear threshold of retention (for example, calcium) and vice versa (for example, water), and a substance may have either threshold, or both (for example, bicarbonate)

Some substances are known as *no-threshold* substances[268] having neither thresholds of retention nor of appearance These materials appear in the urine as long as they are present in the plasma, and there is no plasma level below which they do not tend to be freely excreted. Urea and acetone[1140] exemplify no-threshold substances Other no-threshold substances include paraaminohippurate, phenol red, inulin, sucrose, mannitol, and ethyl alcohol Although a no-threshold substance may be reabsorbed by the tubules, this is thought to be no more than a passive reabsorption or back-diffusion through the tubule walls in response to the concentration gradient between tubular urine and plasma set up by the reabsorption of water (§8 1) No-threshold substances, which are freely filterable, always have a concentration ratio of 1 or more Threshold substances can have a concentration ratio of more or less than (and including) 1 (§3 16). Figure 23 illustrates by analogies the distinction between no-threshold materials and those with thresholds of appearance

The categories threshold and no-threshold cannot be said to include all substances susceptible of renal elimination Ammonia is a case in point Ammonia may have a clearance higher than any determinable level of glomerular filtration but it need not be considered a secreted substance in the same sense as phenol red Because it is formed de novo by the kidney it is more in the nature of a glandular secretion A fraction of urinary ammonia is presumably excreted from the blood[418] but it has not been shown that the concentration ratio in this case can be less than 1, which would establish its threshold nature; and a concentration ratio greater than 1 is nonconclusive. In any case the greater part of ammonia elimination is usually carried out neither as a renal excretion nor as a renal regulation where these terms refer to the plasma content.

The elimination of urinary calcium is also singular despite the fact that it has a threshold of excretion[27, 1176] Presumably it is reabsorbed, judged by its low clearance (Table II) Its concentration ratio is often less than 1, which might suggest that it possesses a threshold of retention However, even where large doses of calcium are given

tends to be of a sodium concentration still lower than the actual plasma concentration If however, the plasma concentration of sodium is above its threshold of retention the urine, regardless of its volume, tends to be of a sodium concentration greater than the actual plasma concentration (for quantifications see §7.4). A man taking a solution *of sodium chloride whose concentration is superthreshold excretes* a urine of superthreshold concentration; intake of a subthreshold solution produces urine of subthreshold concentration.

It may not be amiss to state formally the rules of partition and combination of concentrations However well known these rules may be intuitively, proper attention to them permits one to cultivate a mode of thinking which is helpful in simplifying *diverse problems concerning addition and subtraction of water and solutes, as these* affect body fluid concentrations.

Consider the effects on concentration only when two solutions are mixed, or when one solution suffers a loss, by abstraction, of some solute and some water, for example, where the kidney removes from a volume of plasma, a solution (urine) of the same or different concentration. In the former case we may speak of the addition or combination of solutions of concentrations A and B to form solution of concentration C; *in the latter, we may speak of the partition of solution* A *by subtraction of* solution B to leave solution C

1. Where $A = B$
   (a) $A + B \rightarrow C = A = B$
   (b) $A - B \rightarrow C = A = B$

Thus, from (a) we infer that isotonic solutions (even of different solutes) when mixed in any proportions produce an isotonic solution. From (b) we infer that the produc*tion of a urine whose chloride concentration is the same as that of the plasma water* leaves the remaining plasma water unchanged in chloride concentration.

2 Where $A > B$
   (a) $A + B \rightarrow A > C > B$
   (b) $A - B \rightarrow C > A > B$
   (c) $B - A \rightarrow C < B < A$

Where two solutions of unequal concentration are mixed, as in (a), the resulting solution *is of some intermediate concentration Where a weak solution is subtracted* from a stronger one (b), the remaining solution is the most concentrated of the three Conversely, (c), the removal of a strong solution from a weak one leaves a solution more dilute than either of the others The rules of partition of concentration (1b, 2b, 2c) are those governing the operation of thresholds of retention.

It is this characteristic of urinary function, providing for the maintenance of proper retention of solute relative to water, which insures the level of plasma concentration which we come to take as "normal" and which reflects the activity of the body in regulating its various fluid concentrations (Fig. 19). The threshold of excretion does not have this critical physiological significance, and in addition it is defined somewhat more arbitrarily than the threshold of retention since there is actually no clear level at which substances disappear from the urine.

nected with the plasma protein concentration It is often considered that the physiologically active calcium in the blood is the ionized, diffusible, or "free" calcium, that is, that calcium unbound to protein Thus, in the presence of a low serum protein concentration the "normal" total calcium concentration is a lower value than where serum protein concentration is normal From the nomogram of McLean and Hastings[758] it is possible to deduce a simple equation relating approximately the "normal" total calcium concentration of the serum to the prevailing total protein concentration

$$A_{Ca} = (A_{pr} + 4) \pm 1 \qquad (82)$$

where A_{Ca} is the "normal" total serum calcium in mg per cent and A_{pr} is the total serum protein in grams per cent With a serum protein of 6 per cent, "normal" calcium would be $(6+4) \pm 1$, or 9 to 11 mg per cent Calcium concentrations in mEq /l are obtained by halving the value in mg per cent, that is, in this case, 4 5 to 5 5 mEq /l

7 3 *High and Low Threshold Substances* Cushny[268], treating of thresholds of appearance, distinguished high, medium, and low threshold bodies by comparing the quantities of different substances which had to be present in the plasma in order for urinary excretion of each to occur frankly Neither the threshold of appearance nor this particular method of distinguishing threshold heights has sufficient importance for the urinary function of the kidney to warrant extended discussion or classification of substances in these categories.

However, the threshold of retention can be effectively described by this and more precise nomenclature * For electrolytes whose threshold concentrations are expressed in milliequivalents per liter, that substance has the higher threshold whose numerical value in these units is the higher It has not been established theoretically that there is any "best" way of expressing the threshold concentrations of nonelectrolytes and for this reason the manner in which thresholds of electrolytes and nonelectrolytes can be compared is in doubt

A word should be said about the threshold of water As clearly as any substance, water illustrates the disparity which may exist between thresholds of appearance and retention. Except in certain renal diseases the flow of urine rarely ceases so that there is actually no threshold of appearance for water On the other hand, the concentration of urinary water is clearly either greater than, equal to, or less than that of plasma water concentration when concentrations are expressed, for example,

* Any unqualified reference to the term "threshold" will in further discussion signify "threshold of retention"

intravenously[1176] the concentration ratio may not exceed 1 and *the rate of renal excretion is remarkably* unresponsive to load, indicating that there is little renal regulation of calcium in the sense implied by the concept of threshold of retention It is likely that calcium and some other substances are not importantly regulated as to body content or concentration in body fluids by urinary function alone A concentration ratio less than 1 does not necessarily prove a substance to have a threshold of retention For example, where a substance is bound

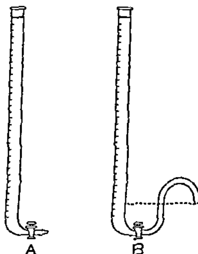


Fig. 23. Analogies for Substances That Have No Threshold (Buret *A*) and Those with a Threshold of Appearance (Buret *B*). Where the level of fluid in the burets with open stopcocks represents the total content (or concentration) of a substance in the plasma, that level is free to fall until nothing is left, in the case of no-threshold substances, when there is no intake A threshold substance, however, present in excess but with no intake, only leaves the body through the kidney until its plasma content falls sufficiently that the plasma concentration is at threshold, indicated by the *horizontal, broken line* At this point the substance no longer leaves in the urine and some is retained in the body

to plasma protein so that some appreciable fraction is not filterable at the glomerulus, it becomes theoretically possible for the concentration ratio for even a secreted substance such as phenol red (80 per cent nonfilterable at plasma concentration of 1 mg. per cent) to be less than 1 at high urine flows. Since calcium is only about 50 per cent nonfilterable, low concentration ratios found for it at relatively low urine flows cannot be accounted for simply as a failure to filter. Calcium is in contrast to hemoglobin which may be 97 per cent nonfilterable (§3 3).

The regulation of the calcium content in plasma is intimately con-

respective concentrations of administered solutions at which equilibrium of intake and output of solute is possible (§7 7)

7 6 *The Time Factor in Isorrhea* The application of the theory of the isorrheic state depends upon a clear recognition of its temporal aspect Isorrheic solutions do not proceed, upon the onset of their administration, to be removed immediately at a rate equal to that of

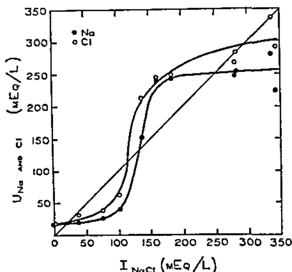


Fig 24 Urinary Sodium and Chloride Concentrations in Man ($U_{Na \text{ and } Cl}$) at the Third Hour of Infusion (fluid intake, 7 cc /min) plotted against concentration of sodium chloride (I_{NaCl}) in the infusion fluid. Critical isorrheic concentrations are those at which the sigmoid curves cross the diagonal isopleth After Wolf [1173]

the intake *Isorrheic solutions are those which are potentially capable of reaching equality of intake and output* [1172] , and equality is isorrhea For sodium chloride solutions all concentrations between the MIC and the LIC are potentially capable of attaining equilibrium of intake and output for both solute and water, except in very young or anesthetized animals [283]. *Solutions below the MIC or above the LIC cannot reach* an equilibrium for both components and hence the characterization, "minimal" and "limiting "

can be maintained without relative retention of x to water (y) is called the *limiting isorrheic concentration* (LIC). With a constant rate of infusion of fluid whose concentration is equal to the LIC,

$$(U_{LIC})_x = I_x \tag{85}$$

A load of x can be reached at which isorrhea is given by

$$u(U_{LIC})_x = iI_x \tag{86}$$

and

$$u = i \tag{87}$$

Thus, with an infusion of solute x whose concentration equals the LIC of x, both solute and solvent reach isorrhea simultaneously (*total isorrhea*), the excretion rates of these tend to reach the same fraction of their infusion rates at time t, and

$$\gamma_x = \gamma_y \tag{88}$$

If the velocity constant, γ, remains constant,

$$\frac{dL}{dt} = iI - \gamma L \tag{89}$$

On integration

$$L_t = \frac{iI(1-e^{-\gamma t})}{\gamma} \tag{90}$$

Since

$$\gamma = \frac{uU}{L} = \frac{C}{b} \tag{91}$$

$$(uU)_t = iI(1-e^{-\gamma t}) = iI(1-e^{-Ct/b}) \tag{92}$$

From equations (85) and (86) it is implicit that

$$\frac{uU_x}{iI_x} = (1-e^{-\gamma_x t}) = \frac{uU_y}{iI_y} = (1-e^{-\gamma_y t}) \tag{93}$$

In addition to the limiting isorrheic concentration there is for some substances a *minimal isorrheic concentration* (MIC). This is the lowest urinary concentration resulting from administered solutions of these substances at which there is no relative retention of water to solute (Figs. 24, 25, 26). For solutions like sodium chloride, isorrhea for both solute and solvent tend to occur together. However, isorrhea for solute alone *(partial isorrhea)* can be obtained with solutions of urea or potassium, and here the *MIC* and the *LIC* are the lowest and highest

the LIC), relative retentions tend to values lower than 1. With solutions below the threshold (and above the MIC) they tend to values above 1 after zero time (Fig 27).

7.7 *Isorrheic Quantities.* Wolf and Ball[1176] introduced the term *isorrheic quantity* (IQ) to describe a rate of excretion of a sub-

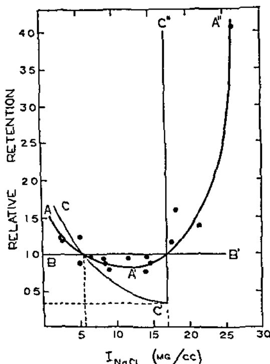


Fig 27 Relative Retention of Chloride as a Function of I_{NaCl} in the Dog Curve *AA'A"* represents the state at the seventh hour of infusion Curve *BB'*

stance which may be maintained steadily equal to its rate of intake They showed that intravenous calcium, infused steadily, had only a single isorrheic quantity which could be termed either the *minimal* or the *limiting isorrheic quantity* (MIQ or LIQ). Chloride, when calcium chloride was infused, showed a MIQ and a *nonlimiting isorrheic quantity*

(Fig. 24), provided that these solutions are respectively above the MIC and below the LIC. In any case, urine flow increases. The effect of these urinary responses is to convert the virtual concentration of the retained solution (load of chloride/load of water) to that of the normal plasma concentration (=threshold of retention=*nonlimiting isorrheic concentration* or NLIC). In the case of solutions at the MIC and the LIC, the attainment of the state where $U=I$ is relatively rapid, a matter of a few hours, and this may occur before the rate of fluid output is equal to the rate of fluid intake. Where infusions are of other concentrations than the MIC or LIC, but within that range, the time at which U becomes equal to I depends on factors such as the rate of infusion, the actual value of I, etc. When a sufficiently long period of infusion has elapsed (up to several days), this time in turn depending on species differences,* body volumes, etc., isorrhea may actually be established[283, 833, 1035, 1170]. This fact argues against the view [841] that the delay in excretion of sodium, chloride, or water from administered solutions of normal saline is due to the lack of appreciable *alteration in plasma composition which such solutions cause.* At isorrhea of both solute and water, the concentration of the urine is equal to the concentration of the administered fluid and the rate of fluid intake is equal to the rate of urine output (presupposing no extrarenal water loss for which, however, appropriate correction can be made). These temporal relations are indicated in figure 26.

The temporal aspect of isorrhea may be examined in other ways, as from consideration of the *relative retention* of solute to water. Let us regard the ratio of the load of solute to the load of water as a virtual concentration of fluid retained from an administered solution, and called the *retention concentration* (L_{Cl}/L_{H_2O}). It is apparent that at zero time, and before urinary action has altered the relative amounts of solute and water in an infinitesimal load of such a solution, the *retention concentration will be equal to I, whatever that may be.* By comparing the retention concentration to the infusion concentration, a *relative retention* ($L_{Cl}/L_{H_2O} \cdot I_{Cl}$) is obtained which at zero time would be 1. From figure 24 it can be deduced that with infusion of solutions whose concentrations are above the threshold concentration (and below

* Renal excretion of salt is more efficient in the dog, in a sense, than in man. An intake of 4 g/kg/day in the dog may be continued for several days without the occurrence of appreciable salt or water retention[635]. In man, less than 0.5 g/kg/day leads to retention of salt and water[458]. Although this presentation ignores the fact that velocity constants (§7.9) are often substantially independent of body weight, there is additional evidence that steady states are more readily obtained in the dog than in man, where salt solutions are infused for several hours[1170, 1172, 1173].

7.8. *Steady State Equations* In §6.5 a steady state equation was derived which described the relations between rates of flow of urinary and intake fluid in terms of threshold and "leakage" concentrations

TABLE XVI

Excretory velocity constants (γ) and critical isorrheic concentrations and quantities of various urinary constituents Minimal, nonlimiting, and limiting isorrheic concentrations (MIC, NLIC, and LIC, respectively) are in mEq or mM/l. Minimal, non-limiting, and limiting isorrheic quantities (MIQ, NLIQ, and LIQ, respectively) are in micro Eq/min. The velocity constant of water may be greater or less than that of Na from NaCl The data in this table are not strictly comparable Original sources should be consulted for conditions under which these were recorded[811, 923, 962, 1170–1173, 1176, 1177]

Loaded Substance	Ion	γ	MIC	NLIC	LIC	MIQ	NLIQ	LIQ
Man:								
PAH	PAH	0.125						
Inulin		0.0086						
NaCl	Cl	0.00067	15	100	340			
NaCl	Na	0.00060	15	150	290			
KCl *	Cl	0.0163						700
NH_4Cl *	Cl	0.00361						
KCl *	K	0.00326	15		70	100		500
$KHCO_3$*	HCO_3	0.00239				140		140
$NaHCO_3$*	Na	0.00180	40					
$NaHCO_3$*	HCO_3	0.00140						
NaCl *	Cl	0.00230	24	100	290			
NH_4Cl *	NH_4	0.00033						
Dog:								
Inulin		0.03						
Na_2SO_4	SO_4	0.0317	50		480	50		
Na_2SO_4	Na	0.0212	50		420	50		
$CaCl_2$	Cl	0.04				8	70	
Urea		0.00497			597			
NaCl	Cl	0.00200		110	290			
$CaCl_2$	Ca	0.00040				2		2
Ca gluconate	Ca	0.00040				2		2
Glucose					<470			

* Orally administered loads. All others intravenous.

A more general equation can now be derived on the theory that if the kidneys maintain normal plasma sodium and chloride concentration during a steady state of intake of sodium chloride and water, the ratio of electrolyte excreted in excess of electrolyte taken in to fluid excreted

(NLIQ) as seen in figure 28 Figure 25 illustrates, for potassium, value which correspond to an MIQ and an LIQ (lowest and highest value where $uU_K = iI_K$, respectively 100 and 500 μEq/min.). Sodium an sulfate, when sodium sulfate is infused, show an MIQ (Table XVI) but no LIQ has yet been established[1177]. Isorrheic quantities ar

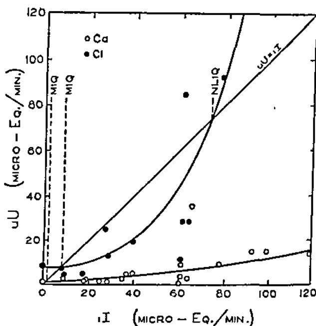


Fig 28. Relation between Rates of Excretion of Calcium and Chloride (uU) and Rates of Intake of Calcium (iI) at the Fifth Hour of Infusion in the Dog Chloride excretion (black dots) is plotted only for infusions of calcium chloride, calcium excretion (white dots) is plotted for infusions of both calcium chloride and calcium gluconate. The diagonal isopleth passing through the origin represents equality of rates of excretion and intake ($uU = iI$). Illustrated are the MIQ and NLIQ The chloride curve is actually a good fit through all points including two not shown on graph at high uU and high iI values After Wolf and Ball [1176].

readily ascertained with certain low or no-threshold substances where the solute's *independence of water during excretion permits the isorrheic* quantity to remain more or less characteristic of the solute at a given load of solute. High threshold substances such as sodium and chloride in sodium chloride depend so much on water in their excretion that the rate of water administration and the water load affect their excretion markedly.

imply equilibrium although an equilibrium represents a steady state. Intake may be steady but output may or may not be so, as the duration of infusion increases Presumably physiological regulations are steadily at work throwing out salt faster than water when the retention concentration *is greater than threshold, and throwing out water faster than* salt when the retention concentration is less than threshold; they act to produce from varying loads of salt and water retention concentrations equal to the normal plasma concentration. Physiological emphasis seems to be placed first upon the regulation of extracellular concentration, then upon the regulation of extracellular volume (§2 4). The

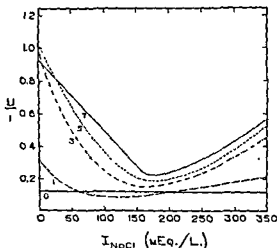


Fig 29 Actual Ratio of Rate of Urinary Flow to Fluid Intake (u/i) in Man Plotted against Concentration of Sodium Chloride (I_{NaCl}) in Infusion Fluid during control period (0 time) and during first, third, fifth, and seventh hours (time printed beside curves) Fluid intake, 7 cc./min *After* Wolf [1173]

maintenance of extracellular concentration implies to some extent that intracellular volume, likewise, is regulated before extracellular volume. We have noted previously (§6 2) the correlation of thirst with decreased cellular volume suggesting that intake as well as renal output is directly concerned with regulating this physiological variable

7.9 *The Velocity Constant,* γ For solutions administered long enough to establish total isorrhea, the velocity constants of solute and water are equal. When the velocity constant of one substance is greater

in excess of fluid taken in should equal the normal plasma concentration or the threshold of retention. Uncorrected for insensible water loss

$$\frac{uU-iI}{u-i}=A_T=\frac{iI-uU}{i-u} \tag{94}$$

and by transposition

$$\frac{u}{i}=\frac{A_T-I}{A_T-U}=\frac{I-A_T}{U-A_T} \tag*{*(95)}$$

For sodium and chloride

$$\frac{u}{i}=\frac{(A_T)_{Na}-I_{Na}}{(A_T)_{Na}-U_{Na}}=\frac{(A_T)_{Cl}-I_{Cl}}{(A_T)_{Cl}-U_{Cl}} \tag{97}$$

The application of these equations is detailed elsewhere[1171-1173] so it suffices here to indicate the curve described by equation (97) in figure 26 and some actual u/i values which have been obtained in experiments of relatively short duration (Fig. 29).

The theoretical curve † does not indicate what the actual value of u/i ought to be at any time but simply what the actual value of u/i would be if the kidneys maintained a constant, normal plasma concentration of sodium or chloride with or without change in the extracellular volume, in the face of an infusion of salt solution. There is less discrepancy between actual and theoretical values when solutions are taken intravenously than when taken orally; and there may be effects of species differences also. Coon, Noojin, and Pfeiffer[240] report diuretic effects of differently concentrated sodium chloride solutions which are at considerable variance with those above. Oral solutions of 0.5 per cent sodium chloride (85 mEq./l.) were found to be the most diuretic of those tested between 0 and 0.9 per cent. No explanation is offered for these results which were obtained following huge priming doses (200 cc./kg. given in two hours).

Where a substance is a no-threshold one ($A_T=0$), the steady state equation (95) reduces to

$$\frac{u}{i}=\frac{I}{U} \tag{98}$$

which is simply the statement of a final isorrhea or equilibrium, that is, $uU=iI$, readily attained by many substances. "Steady state" does not

*Corrected for insensible or extrarenal water loss, w

$$\frac{u}{i}=\frac{I-A_T}{U-A_T}+\frac{A_T}{U-A_T}\cdot\frac{w}{i} \tag{96}$$

† The steady state equation for threshold substances has no validity on theoretical grounds, above the LIC. If it serves with any accuracy in this region it would appear to do so coincidentally.

In addition to permitting the determination of relative retentions and excretions, the velocity constant can be used to establish the critical isorrheic concentrations (MIC, threshold, LIC). Following infusion of solutions whose concentrations are at these critical values, the velocity constants of solute and of water tend to become equal (Fig. 30). Due to the influence of imbalances in solute and water which may have been present prior to an infusion, the velocity constants as calculated in early periods of fluid administration are in error by an amount which tends to decrease with the duration of the infusion Critical concentrations are therefore more readily found from curves of the type in figures 24 and 25

7 10 *The Significance of the Critical Isorrheic Concentrations* Not all substances have three critical urinary concentrations. Threshold substances probably have one or more isorrheic concentrations No-threshold substances, of course, have no NLIC and may or may not have a LIC or a MIC Any substance whose excretion is essentially independent of that of water, except for the fact of being eliminated in that medium, would have no critical urinary concentration, for example, phenol red, or inulin

The *limiting isorrheic concentration* is a critical one because it represents the upper limit of urinary concentration at which a steady state, consistent with effective physiological regulation of solute and water balances, can be maintained This does not carry the implication that viability will be maintained indefinitely since such steady states have not been carried out for periods much greater than 7 hours In these periods unusually high losses of potassium are sustained through urinary excretion[1173] if sodium chloride solutions are administered Although sodium, chloride, and water balances may be consistent with viability in themselves, the importance of other ionic imbalances as secondary complications remains The LIC is not to be confused with the so-called *maximum urinary concentration* (MUC) which is the highest concentration attainable in the urine, when there may be retention of solute relative to water, or when a load of solute may be accumulating excessively in the body (Table XVII)

So long as a continuously administered solution of sodium chloride is just below the LIC, the kidney is able to elaborate a urinary concentration of solute higher than that of the administered solution. In consequence the fluid retained in the body as a load has a retention concentration which steadily decreases toward the threshold concentration. When the concentration of the administered solution is just at the LIC,

than that of another, its rate of excretion is greater per unit load* and it is removed from the body relatively more rapidly. Conversely, the substance *with the smaller velocity constant is retained in the body* relative to the substance with the higher velocity constant. These relations are not necessarily reflected in the absolute excretion rates of either. When loads become negative in the course of time (as for water

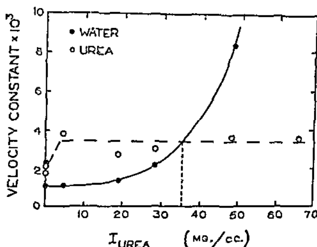


Fig. 30. Velocity Constants of Urea and Water Related to the Concentration of Urea in Infusion Fluid (I_{urea}) after Seven Hours of Infusion in the Dog The LIC of urea is found to be 35 mg./cc. at the point of intersection of the 2 curves, that is, where the velocity constants of urea and water are equal. The presence of sodium chloride at its NLIC or its LIC in the infusion fluids in these experiments may have caused the γ_{H_2O} and γ_{urea} to be different from what they might have been had the infusion fluid contained only urea in isotonic glucose After Wolf [1170].

where absolute dehydration sets in), that substance is the relatively more rapidly excreted which has the *smaller negative* velocity constant. By comparing velocity constants we can ascertain the relative retention and excretion of different substances, a feat not possible with clearances which take no account of the volumes of distribution of the substances, but merely of their plasma concentrations Chloride, for example, can *have a velocity constant higher or lower than urea, whereas its clearance* is never as high as that of urea[1170] under physiological conditions

* Theoretically the velocity constant is equal to the average minute rate of excretion per unit average load ($\gamma = \overline{uU}/\overline{L_t}$). In practice, although the determination of uU in any time period is actually that of $\overline{uU}$, the relative values of γ_a and γ_b are only slightly altered by using L_t instead of $\overline{L}_t$ The velocity constant is usually calculated with no reference to body weight, surface area, etc.

he urinary concentration is also just at the LIC Under these conditions he kidney is operating at its physiological limit, preventing body fluid oncentrations of the solute from rising indefinitely If the administered olution is higher than the LIC, the urinary concentration may also be omewhat higher than the LIC *but it cannot reach a value as high as hat of the administered solution*, and retention of solute relative to vater sets in, presumably without limit Thus, the LIC is a physiologically critical value whereas the MUC is often obtained under what I iave called "metaphysiological" conditions (§1 6) which cannot be naintained steadily for an indefinite time For particular ions of a compound the LIC depends in part on the ion or ions with which it is associated in the body load of that compound[1173]

The consequences of drinking sea water may be considered These are derived, theoretically, from the nature of the LIC rather than the MUC With persistent drinking of sea water, dehydration of the cells progresses rapidly, more so than does that of the extracellular space[336]. This depends on the fact that the saline concentration of the intake fluid (ca 3 5 per cent salt) exceeds the LIC (ca 1 7 per cent salt) so that there is an unchecked increase in the relative retention of salt to water (relative dehydration) That the MUC is, let us say 2 5 per cent salt, has little bearing on the ultimate outcome since even the taking of a solution whose concentration is less than the MUC but higher than the LIC would have the same final effect on cellular dehydration and the production of thirst (§6 2, 6.4) Death from the introduction of large amounts of salt without significant changes in body water results from respiratory failure (nervous system disturbance) with little change in cardiovascular function[335, 1149] This compares interestingly with the effects on the nervous system in water intoxication (relative excess of water over salt) although Albrecht[25] distinguishes "sea water convulsions" from those of water intoxication In anesthetized dogs[1149] no critical lethal plasma concentration of sodium or chloride is observed following forced salt administration These concentrations have been found to rise, respectively, to 200 mEq /l and 190 mEq /l

Toxic effects of many substances, otherwise innocuous, are observed when they are given at rates exceeding that of their possible excretion Intoxication from excessive sodium or potassium ion is described by Guttmann[471], Münzer[799], Arden[47], Winkler et al [1150, 1152], Keith et al [588], Wolf[1170, 1173], and Albrecht[25] With considerable retention of sodium relative to water, there occurs extreme thirst, tremor, convulsions, and respiratory failure With no appreciable retention of sodium relative to water but with large loads of sodium, as in massive infusions of physio

TABLE XVII

Maximum urinary concentrations (MUC). These values are maximal in the sense that appreciably higher values have not been recorded In man the MUC of total solids is approximately 1400 milliosmolal

Substance	Maximum Urinary Concentration		Source of Data
	mEq. or mM /l	Per cent	
Man.			
Cl	411	2 40 (NaCl)	Chaussin[220]
Cl	369	2.16 (NaCl)	Adolph[10]
Cl	342	2 00 (NaCl)	Mainzer and Rachmilewitz[708]
Cl	330	1.93 (NaCl)	Davies et al [285]
HCO_3	374	3 14 ($NaHCO_3$)	Adolph[10]
HCO_3	345	2 90 ($NaHCO_3$)	Mainzer and Rachmilewitz[708]
K	> 200	> 1 49 (KCl)	Wolf[1173]
Total base	500	2 82 (NaCl)	Mainzer and Rachmilewitz[708]
Urea	828	4 96	Adolph[10]
Glucose *	> 830	>15	Duncan[311]
Dog·			
Cl	430	2 51 (NaCl)	Wolf[1170]
SO_4	800	5 68 (Na_2SO_4)	Wolf and Ball[1177]
K	> 400	> 2 98 (KCl)	Winkler and Smith[1154]
Na †	530	3 76 (Na_2SO_4)	Wolf and Ball[1177]
Ca	76	0 42 ($CaCl_2$)	Wolf and Ball[1176]
Ca	53		Mendel and Benedict[769]
Urea	1330	8	Gilman and Kidd[433]
Glucose	720	13	Woodyatt[1180]
Rat.			
Cl	600	3 50 (NaCl)	Adolph[17]
Cl	560	3 27 (NaCl)	McCance and Wilkinson[750]
Urea	2580	15 5	Jacquot et al [565]
Desert Rodent.			
Cl	908	5 30 (NaCl)	Schmidt-Nielsen et al [941]
Total electrolyte	1220	7 13 (NaCl)	Schmidt-Nielsen et al.[940, 941]
Urea	4000	24 0	Schmidt-Nielsen[940]

* In diabetes mellitus. Urinary concentrations of glucose in diabetes are usually 3–5 per cent, rarely over 10 per cent

† The MUC of Na in dehydration or following excess of NaCl is not likely to be so high as the MUC following loading with Na_2SO_4

with less danger of excessive fluid retention, because of the higher u/i values which prevail with these solutions than with isotonic saline Marriott's aim in salt–water restoration for uncomplicated cases is to produce a urine volume in excess of 500 cc. per day, of greater than 0 3 per cent sodium chloride content Determinations of serum electrolyte may give little clue as to what constitutes rational salt–water therapy [172] since normal concentrations may exist in the presence of absolute excesses or deficits of given ions

7 11 *"Osmotic Ceilings" in the Urine* Maximum urinary concentrations of solutes, having a degree of reproducibility, have been called "ceilings" of concentration or osmotic pressure However, constancy is not their cardinal characteristic A number of studies of the properties of ceilings are of interest Chaussin[220] noted the "antagonism" between chloride and urea in urine in the sense that when the concentration of chloride was low there was a correspondingly high concentration of urea This phenomenon was also seen by others including Adolph[10] and Davies, Haldane, and Peskett[285] The latter reported a common maximum urinary concentration for chloride and bicarbonate but thought that the maximum for chloride was relatively independent of the total concentration of the urine or of the maximum of urea or phosphate They found the MUC for both chloride and bicarbonate to be 330 mEq /l and the maximum value of the sum of their concentrations was the same when they were excreted together Mainzer and Rachmilewitz[708] report a common MUC for chloride and bicarbonate at 370 mEq /l Gabrilove[393] found that glycosuria, per se, did not accelerate the urinary excretion of chloride by the patient with diabetes mellitus, yet there was a good correlation between daily urine flow and the sum of the osmolar excretion of chloride and glucose. Similarly, sucrose diuresis superimposed on sodium chloride diuresis lowers the MUC of chloride[537] There appears to be a limit to the total concentration of substances in the urine and it is common that two substances calling for excretion in large amounts lower the MUC for each other However, Gilman and Kidd[433] have observed that where loads of salt given in concentrated solution were excreted, neither mercurial nor urea diuresis in which the rate of urine flow was markedly increased, lowered the osmotic ceiling for salt Nothing is known about "antagonism" at the level of the LIC.

McCance[536, 537, 743, 752] who has examined this subject carefully finds it a complication that not only do certain solutes in the urine exert influence on the maximum concentrations of others by their

the threshold concentration. If the administered solution is of lesser concentration than the MIC the kidney is unable to form urine of still lower concentration than the administered solution and negative salt loads are set up.* However, instead of the plasma concentration and the retention concentration falling, the body suffers an absolute dehydration to an extent which largely protects the plasma from any appreciable fall in sodium or chloride concentration (§6 5). It is not known to what extent plasma concentrations of other substances are similarly protected Since the kidney cannot match by urinary dilution solutions below the MIC, this represents a physiologically critical value. The physiological range of urinary sodium and chloride concentrations, then, is that included between the MIC and the LIC.

It is worth noting that thus far the experimental periods for the determination of the LIC, and particularly the MIC, have been relatively short (7 hours) Although these values are "critical" in the sense discussed they are by no means immutable. Just as the threshold may rise or fall in response to the influence of hormones, drugs, etc, the other critical concentrations probably change with varying physiological stresses and pressures Thus, just as the leakage concentration becomes smaller as the plasma concentration of chloride falls during a salt-free dietary regimen, so might it be expected that the MIC could become smaller as administration of solutions below the MIC is prolonged It is conceivable that the LIC can compensate similarly As McCance[740] has shown, individuals going into severe salt deficit show ultimately a compromise between the regulation of electrolyte concentration and of body volume, that is, although water and salt are lost in proportion in initial stages of salt loss, the osmotic pressure of the serum falls in later stages Equations of steady state (§7 8) presumably do not apply, uncorrected, under these conditions

In recent years there has come a clearer perception in clinical circles of the satisfactory effect obtained from the use of sodium chloride solutions more dilute than normal saline, in the treatment of water and salt depletion Marriott[716], among others, recommends in adults the use of half-isotonic sodium chloride (0 425 per cent) after the major portion of a salt deficit has been corrected In infants one-quarter- or one-fifth-isotonic salt is suggested With solutions only slightly more concentrated than the MIC there is effective salt retention

* For low threshold substances, for example, potassium[736, 1176], where the threshold may be below the MIC and only partial isorrhea is established (equality of intake and output for potassium, not for water) during continuous administration of potassium solutions, the MIC is the lowest concentration above which partial isorrhea obtains and below which potassium output exceeds the potassium intake (Fig 25)

inequality $w > u$ Our analysis suggests a curious rule: *in mammals undergoing ordinary dehydration, and having a concentration ratio for effective osmotic pressure greater than 2, the rate of extrarenal water loss exceeds the concurrent obligatory urine flow* (Table I).

The thirst mechanism we have described illustrates an instance where renal regulation of volume necessarily takes some precedence over regulation of concentration (§6 5) Small urine flows alone, unlike large flows, help to maintain body volume, yet the smaller this flow, the less effective is its normalizing effect on plasma concentration which tends to increase with increasing extrarenal water loss This reasoning leads us to define a unique theoretical and practical significance for the MUC (chiefly of sodium) not shared by the LIC, namely, that the MUC is an antidipsic parameter whose values contribute to the regulation of body volume through their influence on fluid intake and urine output Diabetes insipidus, with its low MUC, points up one consequence of the loss of this antidipsic element Despite the fact that w/u, due to the polyuria, is smaller than normal, $(U-A)/A$ is negative, that is, still smaller Consequently any positive value of w/u, no matter how small, precipitates thirst

A more general form of steady state equation in which w is extrarenal water loss (including sweat) and which includes the rate of extrarenal salt loss, E, is

$$\frac{uU+E-iI}{u+w-i}=A \tag{103}$$

From (103) we derive

$$\frac{w}{u}=\frac{U-A}{A-E/w} \tag{104}$$

In man, nonfecal, extrarenal salt loss is ordinarily ca 0 007 mEq /min Insensible water loss is ca 0 0007 l /min, so that E/w is ca 0 007/ 0 0007=10 mEq /l In those conditions of ambient temperature where w increases, u tends to decrease or remain at minimal values This favors more prompt attainment of the thirst threshold and more prompt replacement of body water, with minimal loss of body volume to the time of drinking With acclimatization to the hot desert in which extrarenal salt loss, E, decreases[297], the factor E/w is decreased This again expedites the physiological regulation of body water in conducing to an earlier thirst than would be the case if E did not decrease The factor w, itself, may be some inverse function of blood osmotic pressure[430], adding further to the complexity of dipsogenic–antidipsic relationships.

urine flow. The dipsogenic element ordinarily is the more potent. Were it not, voluntary drinking in this situation would presumably not ensue.

We can derive important dipsogenic-antidipsic relationships as follows From a steady state equation, including correction for insensible water loss[1172]

$$\frac{uU-iI}{u+w-i}=A \tag{99}$$

where A represents directly or equivalently the normal isotonic osmolality of plasma As an approximation, $A=300$ mOsm/l or 150 mEq sodium per liter U is expressed in comparable units of concentration Where i and iI are zero, we may solve for

$$\frac{w}{u}=\frac{U-A}{A}=\frac{U}{A}-1 \tag{100}$$

Equation (100) expresses the relation of insensible water loss and obligatory urine flow to the maximum, effective osmotic, urinary concentration, if normal concentration of body fluids is to be fixed in the situation described above Actually, under these conditions, A is not maintained constant It steadily increases until the thirst threshold is reached (§6.4) whereupon drinking reverses the trend toward concentration of body fluids We can infer, therefore, that if drinking is to be precipitated, a necessary physiological inequality exists such that

$$\frac{w}{u}>\frac{U-A}{A} \tag{101}$$

For example, in man, if U and A under these conditions were 600 and 300 mOsm/l, respectively,

$$\frac{U-A}{A}=\frac{600-300}{300}=1 \tag{102}$$

By equation (101), therefore, $w>u$ Actual values of w and u might here be 0 7 and 0 35 cc/min, respectively, so that 0 7/0 35=2 Where w is extrarenal loss in a hot environment, w/u is capable of attaining in man[20] a ratio in excess of 300 In the frog which produces a hypotonic urine such that $U<A$, we find by equation (101) that $(U-A)/A$ is negative This reflects the fact that the frog, which never drinks, *gains* rather than loses water through its skin It is interesting to speculate on the necessary adaptations and adjustments which obtain in diverse species of differing surface areas, body weights and temperatures, extrarenal salt losses, etc, as these conform to the

equation (105) that the water intake would have to be raised to enormous daily volumes to bring the effective intake concentration appreciably below the MIC Huge fluid intakes are practically impossible to obtain and are actually undesirable Hence the sharp restriction of salt, being relatively simple to effect, may be accompanied by moderate intakes of water, these acting to bring about an absolute dehydration at the expense of edema fluid

Some mention should be made of the so-called *low salt syndrome* which may occur as a result of intensive efforts to induce a negative salt balance As McCance[740] has shown, too great a forced reduction of body salt leads to a compromise between the maintenance of total osmotic pressure of body fluids and the maintenance of plasma and extracellular volumes Sufficiently rigorous measures will cause a fall in concentration of sodium and chloride in plasma, that is, a breakdown in renal regulation of these ions The signs and symptoms of salt depletion described in §6 3 probably have their origin primarily in a deficit of osmotic pressure in body fluids Deficits of bicarbonate and sodium may give rise to osmotic pressure deficiency wherein the ecuretic response to mercurial diuresis is lost Blumgart et al.[139] describe a patient with these deficits who failed to respond to mercurial diuresis Restoration of acid-base balance by means of sodium bicarbonate led to spontaneous diuresis Excessive administration of water[916], cortical insufficiency (§10 14), diuretic salt lyuresis (see §8 2) as induced by xanthines[470] or mercurial diuretics[946, 1018], restriction of salt absorption by ionic exchange resins[228], and a low salt dietary are all factors favoring an osmotic deficit The injurious consequences which can flow from these diverse conditions are relieved to some or great degree by salt administration, pointing up a common denominator, hyposalemia Harrison and Darrow[492] have indicated that it is chiefly the loss of salt in adrenalectomized dogs which is responsible for the reduced renal function which may exist in these animals

7 14 *Further Views on Volume Edema* Other interpretations of the growth and decay of volume edema, particularly that of congestive failure, have not been wanting Three concepts having some elements in common may be mentioned

First, there are interpretations in terms of clearance analysis Merrill[773] correlated a lowering of both cardiac output and effective renal blood flow in congestive failure. He regarded "forward failure" as a primary cause of edema, rather than "backward failure,"

7.13. *Volume Edema: the Application of Isorrheic Theory.* The researches of Schroeder and Futcher[392, 945] and Schemm[932, 933] have established the effectiveness of a sharp reduction in the daily salt intake in bringing about the reduction of cardiac and certain other partial volume edemas (§2 5). Schemm, particularly, has examined the role of water intake in the presence of edema and finds that, providing the salt is below a certain level of intake (less than 2 grams per day), increased intake of water is not conducive to the formation of edema fluid and, indeed, higher water intakes may be more effective in bringing about the reduction of edema than lower ones

Gorham et al [446] have analyzed this physiological response (absolute dehydration) to low salt and high water intake in terms of isorrheic theory. They noted that although the kidneys in cardiac edema do not appear to possess the same concentrating powers for sodium and chloride as they do in normals, they operate with an approximately normal MIC of 15 to 20 mEq /l. If then, the ratio of dietary salt increment to dietary water increment offered to the kidneys daily is less than the MIC, there should result in steady state an absolutely dehydrating action to some extent proportional to the rate of water intake (§6 5, 7 10) The ratio of salt to water offered to the kidneys was called the "effective intake concentration" (I_e). This value would characterize the salt and water intakes if they were as a saline solution, and it is approximated by

$$I_e = \frac{\text{salt intake—extrarenal salt loss}}{\text{water intake *}} \tag{105}$$

With a salt intake of 4 grams (68 mEq) and a water intake (drunk) of 3 liters daily,

$$I_e = \frac{68-20}{3} = 16 \text{ mEq /l} \tag{106}$$

Thus, a salt intake of 4 grams a day at this rate of water intake will not ordinarily be conducive to the removal of edema since it is equivalent to setting up a steady state at the MIC which will not permit ecuresis or absolute dehydration. When the dietary salt intake is kept quite low (ca. 1 gram per day) the effective intake concentration can be kept decidedly below the MIC and may actually have negative values when the extrarenal salt loss through skin and feces exceeds the intake

This analysis shows how the relative importance of restricting salt and increasing water may be evaluated If salt is not restricted but is allowed from 4 to 10 grams per day, it is readily calculated from

* The quantity of preformed and oxidative water of food is approximately offset by the extrarenal water loss and were omitted for simplicity (Table I).

emonstrated following slightly elevated water intakes, or following ntakes of sodium chloride solution[461], and no small increase in lomerular filtration following increased water intake would offset the arge deficit in filtration that may actually exist. Were it otherwise, he simple mechanical increase in filtration would still be insufficient to ccount for the nice simultaneous adjustments of body content of sodium nd of plasma concentration, without the gratuitous postulation of ubular reabsorptive mechanisms for water different from any presently onceived Even in severe cardiac edema where glomerular filtration nay be low, the leakage concentration (§6 5, 7 10) of sodium in the rine remains much the same as in normal subjects under comparable odium-water intakes And plasma concentration of electrolytes may be essentially normal, precluding the operation of inflexible *Tm* machinery The increased excretion of sodium with increased urine volume due to elevated water intake follows the rule of the steady state equation (§7 8) so long as sodium concentration in the blood is maintained Admittedly there is no theoretical basis for this observation but present nephrodynamic schemes for explaining cause of onset or removal of edema fluid are as empirical and inadequate as are all others They fail, unless fantastically embroidered, to account for the regulation of plasma concentration during all possible changes in body content of water and sodium

Briggs et al [170] confirm the finding of a low filtration rate in cardiac edema but add the observation that patients can regain clinical compensation without in any significant degree increasing filtration rate The ability to excrete sodium was discovered to increase with compensation, and elimination of edema occurred not because of restored filtration rate but because of absolute diminution in tubular reabsorption of water These workers hypothesize that the edematigenous renal response results from *cellular hypoxia* in the presence of a lowered oxygen content of mixed venous blood. The effect of this renal response is thought to preserve blood volume and circulation and, chronically, to lead to edema Earlier, Barach and Richards[61] showed in cardiac edema a diuretic effect of an atmosphere high in oxygen, edema disappeared during, and returned following, high oxygen therapy If Linzbach[665] is correct in regarding as important the oxygen supplied to the tubules by the glomerular filtrate (§8 26), the cellular hypoxia hypothesis gains further support. But if the oxygen tension of kidney tissue is low in cardiac disease (§8 26), the experimental induction of anoxic anoxia in normal individuals favors diuresis and increased excretion of sodium and chloride[48, 101, 202], a fact which appears to complicate the cellular hypoxia hypothesis The

since prevailingly low venous pressures suggested that the low renal blood flow was not due to congestion in the kidney.* Mokotoff, Ross, and Leiter[779] found that effective renal blood flow may be reduced to one-third and glomerular filtration to two-thirds of normal in heart failure They ascertained experimentally that the same percentage of sodium was reabsorbed per unit volume of glomerular filtrate in cardiacs as in normals. However, this conclusion might have been reached on a priori grounds since plasma sodium concentration is not especially abnormal in cardiac patients That the tubules reabsorb sodium and water in the same proportions as they exist in the glomerular filtrate is not an explanation but merely a descriptive statement of a condition which could not be otherwise. By the tubular maximum hypothesis (§8 1) of Wesson, Anslow, and Smith[1123, 1124] *it could be said that in the face of reduced glomerular filtration, the Tm* of sodium in the distal tubule permits the reabsorption of a larger percentage of filtered sodium than normal, with resulting diminution in absolute sodium excretion, in order to account for the positive balance of this ion during edema formation

Clearance-based hypotheses lose force when they imply that a single ion, namely, sodium, lies at the root of the edema problem. Retention of sodium in combination with sulfate does not favor edema formation [1177] Manifestly, water and certain other ions have a place in the edema picture and are of importance How shall we explain the effectiveness of increased water intake in removing edema[446, 932, 933] by clearance theory? In order to remove edema, no less than two negative balances must be established, that of water and that of sodium † If elevated water intake increased glomerular filtration and there were no tubular reabsorptive changes, then some augmented loss of water and sodium would occur, according to current renal theory However, no significant changes in inulin clearance have been or are likely to be

* Much earlier Starling[1023] stated that the causation of cardiac edema lay in both heart-pump failure with fall in arterial pressure, and a rise in venous pressure, together with *a fall in capillary pressure peripherally as in the kidneys and intestine* Consequent increased fluid absorption by these capillaries was taken to favor positive water and salt balances which culminate in edema (§1 18).

† This is not to imply that sodium is more "important" than chloride or bicarbonate, for example The argument that sodium is more important in relation to water balance than chloride, based on the latter's replaceability by bicarbonate (as when either sodi
inconclusive. It
behave similarly
Sodium and sulfate act quite differently with respect to water, and sodium in this combination never favors edema formation (§7 3, 7.18).

demonstrated following slightly elevated water intakes, or following intakes of sodium chloride solution[461], and no small increase in glomerular filtration following increased water intake would offset the large deficit in filtration that may actually exist. Were it otherwise, the simple mechanical increase in filtration would still be insufficient to account for the nice simultaneous adjustments of body content of sodium and of plasma concentration, without the gratuitous postulation of tubular reabsorptive mechanisms for water different from any presently conceived Even in severe cardiac edema where glomerular filtration may be low, the leakage concentration (§6 5, 7 10) of sodium in the urine remains much the same as in normal subjects under comparable sodium-water intakes And plasma concentration of electrolytes may be essentially normal, precluding the operation of inflexible *Tm* machinery The increased excretion of sodium with increased urine volume due to elevated water [illegible] equation (§7 8) so long as so[illegible] tained Admittedly there is [illegible]ation but present nephrodynamic schemes for explaining cause of onset or removal of edema fluid are as empirical and inadequate as are all others They fail, unless fantastically embroidered, to account for the regulation of plasma concentration during all possible changes in body content of water and sodium

Briggs et al [170] confirm the finding of a low filtration rate in cardiac edema but add the observation that patients can regain clinical compensation without in any significant degree increasing filtration rate The ability to excrete sodium was discovered to increase with compensation, and elimination of edema occurred not because of restored filtration rate but because of absolute diminution in tubular reabsorption of water These workers hypothesize that the edematigenous renal response results from *cellular hypoxia* in the presence of a lowered oxygen content of mixed venous blood The effect of this renal response is thought to preserve blood volume and circulation and, chronically, to lead to edema Earlier, Barach and Richards[61] showed in cardiac edema a diuretic effect of an atmosphere high in oxygen, edema disappeared during, and returned following, high oxygen therapy If Linzbach[665] is correct in regarding as important the oxygen supplied to the tubules by the glomerular filtrate (§8.26), the cellular hypoxia hypothesis gains further support But if the oxygen tension of kidney tissue is low in cardiac disease (§8 26), the experimental induction of anoxic anoxia in normal individuals favors diuresis and increased excretion of sodium and chloride[48, 101, 202], a fact which appears to complicate the cellular hypoxia hypothesis The

effects of histotoxic anoxia as by cyanide have not yet been related to the edema problem.

Borst[153, 154] cogently states his conviction that an essential factor in the genesis of edema is a *regulation* of urinary excretion of water and sodium chloride by the kidney which effects the maintenance of an adequate cardiac output. Water and salt are retained, in this view, when the amount of circulating blood is insufficient to maintain a normal cardiac output Such retention is not considered "disturbed" renal function but rather an accommodation of function in the regulation of body volume, venous pressure, and cardiac output. Salt retention is regarded as one of the first, most constant, sensitive, and essential manifestations of forward failure (decreased cardiac output from any cause). In support of this view it is shown that, following hemorrhage, there is a cessation of chloride excretion and an increase of potassium excretion, which favor the maintenance or raising of blood volume. Rapid transfusion of blood so as to increase blood volume results in increased chloride and water excretion the effect of which tends to minimize the possible increase in blood volume. Borst opposes Merrill's hypothesis because of the improbability that hypoproteinemic edema would have the same cause as cardiac edema; if cardiac output is not altered in the same way in cardiac as in renal edema, forward failure *cannot* be the *sole* diathetic condition in both. Borst is one of few to acknowledge the renal regulation of blood volume through water and salt excretion on a priori grounds, not fearing the consequences of *having no immediate "explanation."*

The lack of diuretic response to water loads in salt deficient animals [59, 1143], the oliguresis following the induction of a hypotonic serum *by means of isotonic glucose given intraperitoneally*[281], the minimizing of distortion by the kidney (§2 4), and the case made out elsewhere in this book for the regulation of body volume by the kidney are all *consonant* with Borst's view.

Renal Congruence Principles of Ion Excretion

7.15. The renal regulation of solutes and water as a prime urinary function of the kidney can be treated in terms of retention and excretion, both absolute and relative. At present, detailed exposition of the manner in which the renal units handle these substances is not conducive to the elucidation of the physiological "laws" of excretion which govern the interrelations among different substances. Not all of the "fundamental" facts which gladden the biochemist excite the physiologist (and the vistas of the physiologist do not always favorably impress the biochemist). Even in the realm of solute excretion, possibly the

field of the greatest total effort of renal physiologists, few generalizations can be stated. Studies of renal retention and excretion of water are usually filed under "antidiuresis" and "diuresis" and are rarely integrated with the retention and excretion of solutes. While it is still convenient, unfortunately, to treat the renal retention and excretion of solutes and water separately for the most part, there are some integrable aspects which can be explored here.

We have previously remarked on the hypotheses dealing with the "dominant ion" in water retention (§2.2, 2.3). Widal[1138, 1139] believed that chloride was of the first importance while Blum[132–137] and Gamble[402] supposed that sodium should be so characterized.

TABLE XVIII

Velocity constants, γ, in man. The relative excretion rate is the ratio of the velocity constant of an ion to the velocity constant of sodium from sodium chloride, the latter taken arbitrarily as unity[1173]

Substance Administered	Ion	γ	Relative Excretion Rate
KCl	Cl	0.0163	27.2
NH_4Cl	Cl	0.00361	6.01
KCl	K	0.00326	5.44
$KHCO_3$	HCO_3	0.00239	3.98
$KHCO_3$	K	0.00230	3.84
$NaHCO_3$	Na	0.00180	3.00
$NaHCO_3$	HCO_3	0.00140	2.34
NaCl	Cl	0.00067	1.12
NaCl	Na	0.00060	1.00
NH_4Cl	NH_4	0.00033	0.55

The author[1172, 1173, 1177] on the other hand, and for reasons previously mentioned, has rejected the view that any one ion, per se, exerts a unique and characteristic effect on the excretion or retention of water or a load of that ion. The behavior of any ion is thought to depend to a variable degree on the electrically associated, loaded ion, and on the existing balances and body contents of other solutes and water. It is known that solutions of sodium chloride or sodium bicarbonate may be edematigenous at some times but not at others (depending on effective intake concentrations). The examples of substances like sodium sulfate and potassium chloride which so readily leave the body with water can be used to argue against the idea that either the sodium or the chloride alone can be responsible for the water retention seen with administration of physiological saline. In Table XVIII the

relative excretion rates of a number of ions are shown for their administration with different associated ions. These provide little evidence in favor of complete ion dominance.

7.16 *Thresholds of Ions of Like Sign.* While there may be no necessary relation between concentrations of molecular and ionic species in the serum, for example, between azotemia and hypochloremia[599], it is well known that definite relations exist between certain ions of like sign Bodansky and Modell[142] showed in dogs how the urinary excretion of bromide or chloride ions in more than negligible amounts depends upon the concentration of the total plasma halide, no appreciable excretion occurring below halide levels of 108 mEq/l (the threshold of retention for chloride in the dog) except when mersalyl (salyrgan) or theophylline is administered A formula for indicating the extent of differential excretion of bromide and chloride was given as

$$K = \frac{U_{Br}/U_H}{A_{Br}/A_H} \tag{107}$$

where K is a "constant" and H refers to total halide concentration By transposition

$$K = \frac{U_{Br}/A_{Br}}{U_H/A_H} \tag{108}$$

Multiplying through by u, we can approximate

$$K = \frac{uU_{Br}/A_{Br}}{uU_H/A_H} = \frac{C_{Br}}{C_H} \tag{109}$$

The ratio of concentration ratios or clearances, K, ranged from about 0 7 to 1 0 during the periods of diuresis following large injections of sodium chloride, sodium bromide, or subcutaneous injections of mersalyl or theophylline. In subsequent periods, K fell to a value of about 0 4

Bromide apparently mimics chloride, passing as the latter so far as the kidney is concerned to a considerable though variable degree Both ions share a common threshold of retention for total halide and may be said to possess a certain *renal congruence* In spite of high concentrations of bromide in the plasma, little is excreted if the total halide is below its threshold of retention, and the thresholds of bromide and of chloride are interrelated. Each ion lowers the threshold of the other and raises its own, as it is loaded on the body

Sulfate and chloride thresholds are also interrelated According to Amberson[42] it is not possible to reduce the plasma chloride to less than 75 per cent of normal in cats by sulfate–Ringer infusion (where

chloride is replaced by sulfate) since the urine becomes essentially free of chloride (yet plasma chloride can be reduced to 6 per cent of normal by plasmapheresis with life maintained for short periods). It has not been definitely established that the chloride threshold in this situation is lowered since the concentration ratio of chloride during sulfate diuresis is less than one It would appear that the plasma chloride concentration during sulfate diuresis is below its threshold, but the actual chloride threshold is not exactly known[449, 944]. Schwartz, Smith, and Winkler[950] have noted that there may be an inhibition of chloride excretion at least temporarily when loads of chloride and sulfate are being excreted simultaneously This was taken to mean that sulfate increased the chloride threshold during this initial period, a conclusion arrived at also by Conway and Kane[239]. Conversely, chloride is said to lower the threshold for sulfate. Lotspeich [688] who has determined the threshold of sulfate in the dog to be between 2 and 4 mEq/l (thresholds of appearance and retention are here of the same order of magnitude) finds that hypertonic sodium chloride infusions lead to a decrease in the tubular capacity to reabsorb sulfate This would appear to confirm the lowering of the sulfate threshold by chloride under these conditions

Nitrate can replace plasma chloride Hiatt[541] finds that intravenous sodium nitrate, coupled with a low chloride diet, can cause continued loss of chloride even when the plasma chloride has been reduced far below its usual threshold of excretion Dogs were caused in this way to lose up to 70 per cent of their total body chloride. Nitrate was promptly excreted except at low chloride concentrations when it was excreted more slowly There was an increase in serum bicarbonate and pH but a decrease in osmotic strength. Unlike animals on a salt-poor diet alone, these animals do not have salt hunger

Relations between plasma bicarbonate and chloride are known[396]. Since the total cation of the plasma remains relatively constant under many conditions in which the pattern of the anions may change, it is to be expected that a lowering of plasma bicarbonate or chloride is likely to be accompanied by a corresponding rise in chloride or bicarbonate. Pitts and Lotspeich[865] consider that the renal thresholds of appearance of these two ions are interrelated in some manner, the effect of which is to maintain the sum of their plasma concentrations within nearly normal limits. They submit data showing that a load of chloride tends to increase the excretion of bicarbonate and vice versa However, some of my experiments[1173] carried out for longer time periods suggest that there may actually be a diminished excretion of chloride when bicarbonate is loaded on the body The fact that plasma chloride

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The ratio of concentration ratios or clearances, K, ranged from about 0.7 to 1.0 during the periods of diuresis following large injections of sodium chloride, sodium bromide, or subcutaneous injections of mersalyl or theophylline. In subsequent periods, K fell to a value of about 0.4.

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The difference in diuretic behavior between isotonic sodium sulfate and isotonic sodium chloride solutions[703, 1177] is of interest in this connection The former solution behaves essentially the same as an equal volume of water alone, when given intravenously, in its effect on urine flow. Indeed, all solutions below the LIC of sodium and sulfate (420 to 480 mEq /l) act similarly, diuretically It is of descriptive and possibly fundamental importance to observe that whereas in the case of sodium chloride solutions we deal with a solute having a high threshold of retention, we deal in the case of sodium sulfate solutions with a solute having an extremely low threshold The complex and physiologically necessary interdependence of excretion between water and sodium chloride has been exhaustively examined previously in this chapter and quantitative relations have been stated in steady state equations In these terms one can describe and predict the diuretic activities of sodium chloride solutions of any concentration, the isotonic sodium chloride merely being one of an infinite number of salines of differing diuretic potency With sodium sulfate, by virtue of its having no appreciable threshold, there is no necessary interdependence of the excretions of water and solute so long as urinary concentrations remain below the LIC (Fig 19) Thus, we could well expect that isotonic sodium sulfate would act little differently than an equal volume of water alone, in regard to diuresis (although water diuresis is less lyuretic) Just as no-threshold phenol red[245, 918] or low threshold calcium excretion[1176] is independent of water excretion, so is that of low threshold sodium sulfate[1177] It may be noted that isotonic solutions of different solutes have no critical significance for renal excretion derived from the isotonic property, of itself

7 19 *The Principle of Replacement, and Others* As noted in §7 16 a surfeit of ions of one species and sign may lower the threshold for ions of another species but of like sign Perhaps because of some physiological congruence between ions, the kidney handles them in a manner that favors the replacement of one ion in the plasma by another However, the lowering of the threshold of one ion by the surfeit of another need not depend primarily on renal activity We might by transfusion or plasmapheresis replace a fraction of the body chloride by bromide and establish the chloride at once at a new, lower threshold Again, the threshold of no ion having one is characteristic and independent, a threshold depends on the replaceability of the ion in question and on the body content of other ions, solutes, hormones, etc A

When

$$\Sigma(CAT)_{\lambda T}=0 \tag{113}$$

and

$$\Sigma(AN)_{\lambda T}=0 \tag{114}$$

$$\Sigma(CAT)_{T}=\Sigma(AN)_{T} \tag{115}$$

Ions of a given sign in surfeit (or otherwise), require in their excretion an electrically equivalent number of ions of opposite sign which may behave as if they also were in surfeit. Thus, sodium and sulfate

TABLE XIX

Anion and cation balance of normal human plasma. The average water content of normal human plasma is about 935 g. per liter. The value, E, in the table is taken as the difference between the total determined base and the total determined acid ($Cl + HCO_3 + \text{Protein} + PO_4 + SO_4$). It includes anions contributed by weak organic acids[798]

Cation	mEq./l.	Anion	mEq./l.
Na	138 0	Cl	105 0
K	4 5	HCO_3	25 0
Ca	5.2	Protein	16 0
Mg	2 0	PO_4	2 2
		SO_4	0 5
		E	1.0
Total base	149 7	Total acid	149 7

following hypertonic sodium sulfate solutions are excreted essentially at the same rate[156, 950, 1177] although with respect to thresholds sulfate is in much the greater relative excess It is a corollary of this principle that ions present in the body which we are inclined to regard characteristically as threshold, actually consist of two or three fractions, namely, high threshold, low threshold, and no-threshold Since sulfate is a low threshold substance, the addition of a load of sodium sulfate to the body provides a load of "low threshold" sodium This is distinguished from the "high threshold" sodium constituting the bulk of the body sodium by the fact that the urinary excretion of the former is a function of the plasma sulfate and not the plasma sodium [156, 950, 1177] Similarly, the low threshold potassium of potassium chloride determines a low threshold fraction of high threshold chloride [1154, 1173].

The difference in diuretic behavior between isotonic sodium sulfate and isotonic sodium chloride solutions[703, 1177] is of interest in this connection The former solution behaves essentially the same as an equal volume of water alone, when given intravenously, in its effect on urine flow Indeed, all solutions below the LIC of sodium and sulfate (420 to 480 mEq /l.) act similarly, diuretically It is of descriptive and possibly fundamental importance to observe that whereas in the case of sodium chloride solutions we deal with a solute having a high threshold of retention, we deal in the case of sodium sulfate solutions with a solute having an extremely low threshold. The complex and physiologically necessary interdependence of excretion between water and sodium chloride has been exhaustively examined previously in this chapter and quantitative relations have been stated in steady state equations In these terms one can describe and predict the diuretic activities of sodium chloride solutions of any concentration, the isotonic sodium chloride merely being one of an infinite number of salines of differing diuretic potency With sodium sulfate, by virtue of its having no appreciable threshold, there is no necessary interdependence of the excretions of water and solute so long as urinary concentrations remain below the LIC (Fig 19) Thus, we could well expect that isotonic sodium sulfate would act little differently than an equal volume of water alone, in regard to diuresis (although water diuresis is less lyuretic) Just as no-threshold phenol red[245, 918] or low threshold calcium excretion[1176] is independent of water excretion, so is that of low threshold sodium sulfate[1177] It may be noted that isotonic solutions of different solutes have no critical significance for renal excretion derived from the isotonic property, of itself

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normal threshold is "normal" when appropriate, critical environing conditions are "normal."

Electroneutrality, ion-surfeit equivalence, and replacement are three principles known to govern the urinary function of the kidney. But there is not sufficient data available yet which can be analyzed by these principles to establish quantitatively their application. It is not unlikely that other principles remain to be formulated. Without them, knowledge of the excretory characteristics of urinary constituents will not be satisfying to the urinary physiologist. If a load of sulfate enjoys preferential excretion over a load of chloride[950] it may thereby displace chloride from the urine. We can guess at this consequence from particular information concerning the behavior of sulfate and chloride in other respects, and from the principle of electroneutrality Yet we have no clear guide to suggest that a load of sulfate will be preferentially excreted One of the important missing links is that which should connect the urinary excretion of solutes with the urinary excretion of water, particularly under physiological conditions Until this is found or forged, solute excretion and water excretion will too often remain separately categorized and unintegrated Points of tangency between the two categories seem to lie in the MUC and the LIC, obscure though their mechanisms may be, and in steady state equations which relate the excretory characteristics of water and solute But the physiologist still cannot predict well the urinary patterns of excretion when loads in any combination of solutes and water are sustained.

7 20. *Calcium Excretion* It is of interest to review some of the peculiarities of calcium excretion through the kidney, a matter which has received little systematic study. Ordinarily there is little relation between the renal excretion of calcium and water. The concentration ratio for calcium is usually greater than 1[100] but with diuresis this may drop to extremely low values (Table II). Calcium excretion does not follow closely variations in urinary flow[143, 420] although some correlation has been observed[440, 1176]. Alone, these facts mark calcium as different from substances of the inulin type (whose concentration ratio never falls below 1), from those of the acetone type (whose concentration ratio is always essentially 1), and from the urea type and sodium type whose excretory patterns are so intimately tied to those of water. We may go further. Intravenous calcium has no specific diuretic influence[1176] and is thus distinguished from urea, glucose, sulfate, and other lyuretic diuretics It is not, like

potassium or phenol red, rapidly excreted per unit load (that is, its *velocity constant of excretion is small*). *In short, its excretory pattern* does not resemble that of water or any other substance whose body content is extensively regulated by renal activity. In its low rate of excretion per unit load and in its low threshold of excretion, it is like hemoglobin; in its increased renal elimination following increased acid ingestion and elimination, it is like ammonia[217, 354, 437, 438]; and in its increased elimination following administration of hypertonic solutions [1177] it is like potassium.* None of these characterizations appear now to contribute basically to our understanding of the renal excretion of calcium. Neither is there any assurance that consideration for calcium–protein (§7 2) and calcium–phosphorous complexes[637] in *the blood will indicate that calcium is actually renally congruent to* other substances

The crowning complexity probably lies in the action of hormones on calcium excretion. Administration of parathyroid hormone leads to increased urinary excretion of calcium and phosphorus, these ultimately derived from the bones[462]. It has been thought that the hormone primarily decreases the phosphate threshold[26, 27, 185], leading to increased urinary excretion of phosphate[1075] and a fall in plasma phosphate concentration[493]. A supposed necessary inverse relation between serum calcium and phosphate concentration, based on solubility products, has been taken by Albright and Ellsworth[27] to account for the consequent increase in *plasma calcium concentration and the* subsequent increase in urinary excretion of calcium. But no necessary inverse relation between calcium and phosphate concentrations exists [975] if we judge from the observations that after parathormone, serum calcium as well as phosphate may fall[342], that vitamin D administration produces elevation of both serum calcium and phos*phate*[493], and that after intravenous calcium, the threshold of phosphate is apparently raised (its urinary excretion is diminished while its serum concentration may be increased) while serum calcium is elevated

Clearance analysis has not provided any clear answer as to whether the excretion of calcium

* Curiously, the urinary excretion of calcium may increase more readily following administration of substances like acid[353], magnesium[769], and hypertonic sodium sulfate[1177] than following its own administration[1176]

FACTORS AFFECTING THE REACTION OF THE URINE

7.21. *Thresholds of Hydrogen Ion and Bicarbonate.* In normal men the urine becomes more alkaline than the blood when plasma bicarbonate exceeds its threshold of retention[836]; and the critical level at which urine pH is equal to plasma pH, when expressed in concentration of hydrogen ions, is a threshold of retention for hydrogen ion (ca 4×10^{-8} mEq./l. at pH 7.4). It may be observed in the dog that when urinary pH is below plasma pH, the concentration of urinary bicarbonate tends to be lower than that of plasma bicarbonate and when urinary pH is above plasma pH, the reverse is the case These are expected correlations between thresholds Urinary function calls for compensatory elimination of both hydrogen and bicarbonate ions, taking away from the body a solution of either, more dilute than the plasma in order to concentrate it, or more concentrated than the plasma in order to dilute it (§7.2)

In ordinary aciduria the bicarbonate concentration of the plasma is below its threshold Metabolically, the normal food intake is effectively the equivalent of a steady intake of acid which keeps the concentration of plasma bicarbonate lower than it would tend to be on a neutral or alkaline intake. The titratable acidity of the urine in steady state therefore closely measures the potential acid intake.

7.22 *Diuresis* Water diuresis (Fig 31) or diuresis following administration of different neutral salts such as sodium sulfate, sodium chloride, or sodium nitrate tends to induce alkalinization of acid urine [213, 267, 919, 1173, 1177] Diuretics such as caffeine, urea, and diuretin have been reported to lead to alkalinuria[580] Eggleton[320] states that injection of hypertonic sucrose or sodium sulfate in man results in increased acidity of the urine with a decrease in buffer output, while the diuresis of strong urea solution gives a decrease in acidity with increase in buffer output. An inverse relation between urinary acidity (hydrogen ion concentration) and buffer output was suspected At high urine flows the inverse relation may be masked by a "flushing out" effect on buffers, which may signify that the body can get rid of more acid ions without lowering the urine pH if more buffer is excreted It has been reported by Barclay et al.[70] that the pH of urine during water diuresis tends toward 6 9 irrespective of its initial pH level, but clarification is needed at least of the effect of the concurrent state of systemic acid–base balance on this apparent pH asymptote in diuresis.

7.23. *Systemic Acid-Base Balance.* Systemic alkalosis is brought on by a sufficient intake of alkalinizing substances such as sodium or potassium bicarbonate; systemic acidosis, by sufficient intake of acids or

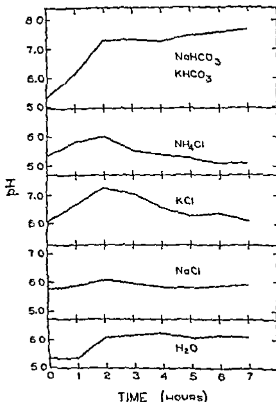


Fig 31 Average Course of Urinary pH in Man during a period of 7 hours of continuous administration of water and of solutions of the substances indicated Fluid intake, 7 cc /min., four bicarbonate solutions between 21 and 134 mEq /l ; three ammonium chloride solutions between 43 and 127 mEq /l ; four potassium chloride solutions between 41 and 168 mEq /l., five sodium chloride solutions between 36 and 338 mEq /l. After Wolf [1173]

acid-forming salts Loss of acid or alkali with body fluids also causes these reactions Ordinarily the reaction of the urine can be inferred from the concurrent state of systemic alkalosis or acidosis (§7.21). However, aciduria may coexist with systemic alkalosis[741, 742, 1089] so severe that administration of bicarbonate to a patient with such

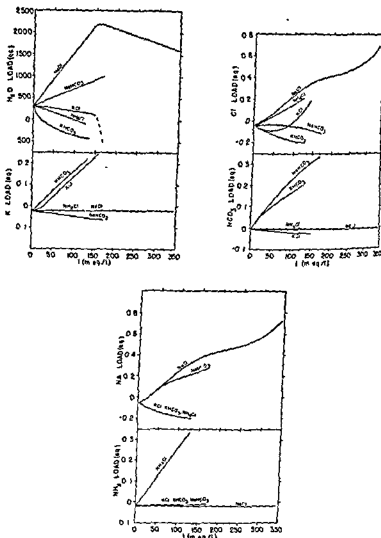


Fig. 32 Loads of Water (Net), Potassium, Chloride, Bicarbonate, Sodium, and Ammonia in Man at the Seventh Hour of Continuous Infusion or Oral Administration (at 7 cc./min) of Solutions whose concentrations are plotted on the abscissae (*I*). Each substance administered is printed beside its curve. Sodium chloride was intravenous; all others oral. The broken line for potassium chloride in the upper left hand graph indicates the severe ecuresis or absolute dehydration induced until vomiting stopped the experiment at the 349th minute. The "load" of ammonia was computed from intake and output without regard to its existence in the body. After Wolf [1173].

kidney enabling fixed base, chiefly sodium, to be conserved by the body through the regulated substitution of ammonium ion for plasma base ions, in covering acid radicals as they enter the urine.

Briggs[166–168] rejects this "classic" concept and has brought together experimental evidence to show that the renal ammonia mechanism has little to do with the regulation of the systemic acid-base balance He holds that ammonia excretion increasing with decrease in

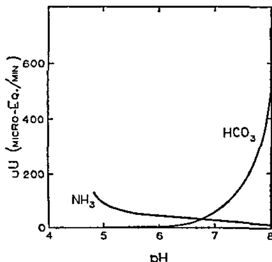


Fig. 35 Rate of Excretion (uU) of Ammonia and of Bicarbonate in Man Plotted against the pH of Urine. After Wolf [1173]

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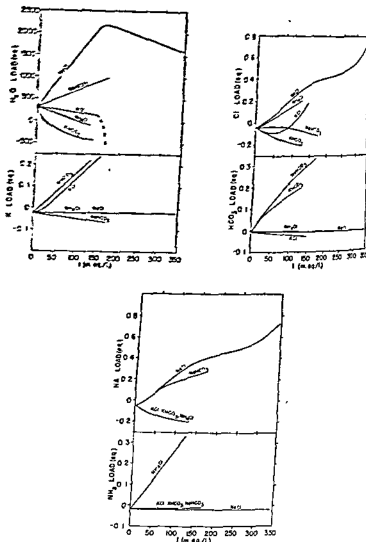


Fig. 32. Loads of Water (Net), Potassium, Chloride, Bicarbonate, Sodium, and Ammonia in Man at the Seventh Hour of Continuous Infusion or Oral Administration (at 7 cc./min.) of Solutions whose concentrations are plotted on the abscissae (*I*). Each substance administered is printed beside its curve. Sodium chloride was intravenous; all others oral. The broken line for potassium chloride in the upper left hand graph indicates the severe ecuresis or absolute dehydration induced until vomiting stopped the experiment at the 349th minute. The "load" of ammonia was computed from intake and output without regard to its existence in the body. After Wolf [1173]

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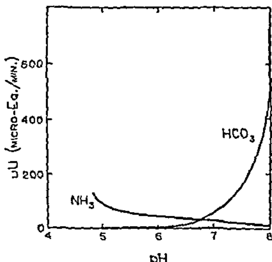


Fig 55 Rate of Excretion (*uU*) of Ammonia and of Bicarbonate in Man Plotted against the *p*H of Urine After Wolf [1173]

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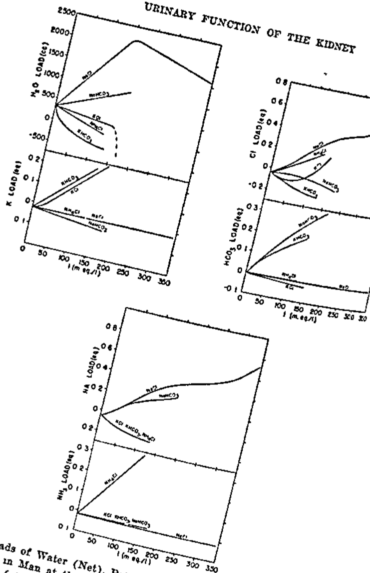


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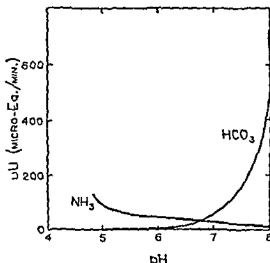


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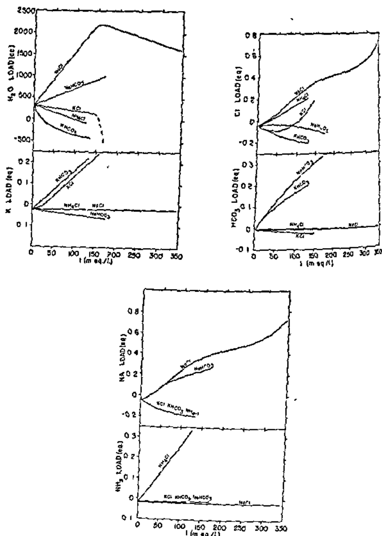


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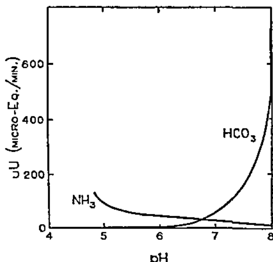


Fig 33 Rate of Excretion (uU) of Ammonia and of Bicarbonate in Man Plotted against the pH of Urine After Wolf [1173]

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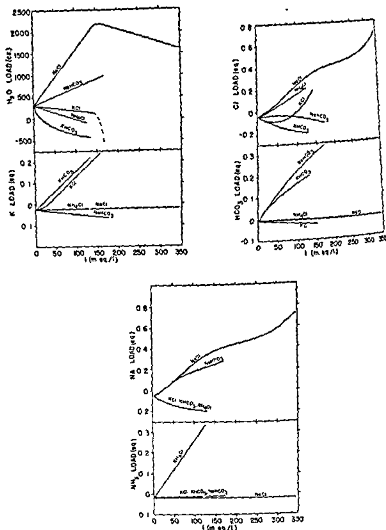


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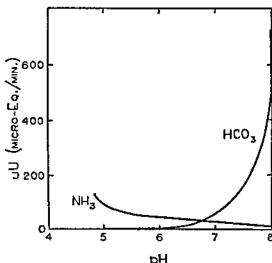


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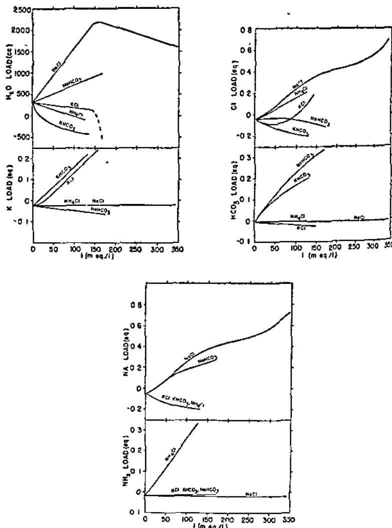


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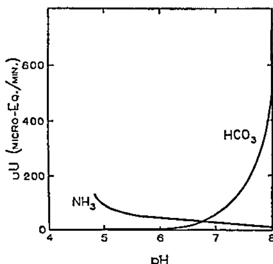


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is that between urinary *p*H and ammonia excretion * (Fig. 33). It has been shown that in acidosis there may be a far greater loss of fixed base than can be replaced by ammonia excretion. The latter in fact is often too late in onset to be very effective There is also no clear relation between ammonia excretion and the concentration of fixed base in the body fluids, as opposed to the body content of fixed base

The augmenting excretion of ammonia under pressure of prolonged acid intakes is conceivably an adaptive response not essentially different, in the larger biological sense, from that of the formation of calluses on the hands following hard manual labor or the decreased expenditure of salt in the sweat after acclimatization to the desert[297] Admittedly a high rate of excretion of ammonia serves to eliminate larger quantities of potential acid than a low rate of ammonia excretion, other things being equal. But it is possibly a physiological sophism to entertain the view that ammonia is essential for the regulation of systemic acid-base balance by conserving fixed base. Just as the concept of "water conservation" (§10.10) must be considered in relation to other physiological functions and not defined in isolation, so it may be wise to determine if there are not higher interests of the organism involved in losing fixed base, however it may do so. Ammonia formation is a normal physiological process, just as is loss of fixed base where there are appropriate intakes of potential acid of food or of fixed base. Preoccupation by physiologists with the consequences of renal activity for acid-base balance without consideration of the compensatory possibilities inherent in modified intakes of base or potential acid, or without consideration of other principles of body economy, is not in keeping with proper scientific perspective and is, I think, an unscientific parsimony. Neither is it conducive to a view compatible with the known facts. Many critical experimental studies remain to be made on the interrelations of ammonia excretion with that of other substances, and cogent interpretation should be possible for these without the afflatus of the "conservation" concept

* Ammonia excretion normally tends to be higher as urinary *p*H decreases The more acid the urine, the less acid the reabsorbate. It is of interest to note that the optimum *p*H of glutaminase[45] and of l amino acid oxidase[123] catalyzing the production of ammonia from several amino acids, is alkaline. Dog kidney glutaminase is entirely inhibited in action below *p*H 6. Any correlation of increased ammonia production in the kidney with increased alkalinity of reabsorbate is at least consistent with the Briggs hypothesis Activity of renal glutaminase in tissue slices (dog or cat) is stimulated by pyruvate, phosphate[803], and β hydroxybutyric acid A possible relation is suggested between this fact and the increased formation of ammonia in diabetic acidosis Decreased ammonia production in nephritis may stem from a deficit of glutaminase

7 27. *The Acidification of the Urine.* The adjustment of urinary pH is intimately linked to the renal regulation of other electrolytes Hydrogen ions attain their particular concentrations in urine by means which are neither well known nor readily subjected to the finest analysis We know that when the plasma pH is appreciably above 7.4, that of the urine tends to be still higher. When plasma pH is below this value, that of the urine tends to be still lower The threshold of retention in terms of pH is thus approximately 7 4 and in terms of hydrogen ion concentration, 4×10^{8} mEq /l Percentually, the regulation of hydrogen ion concentration in the plasma is not better than that of other plasma constituents

Pitts and his associates[863, 864, 866, 934] have indicated that the phosphate reabsorption theory and the carbonic acid filtration theory are inadequate to account for the quantity of acid which can be excreted in acidosis Simultaneous estimates of glomerular filtration rate and reabsorption and excretion of mono- and dibasic phosphate and carbonic acid suggest that the quantity of acid found in fully formed urine can far exceed that which enters the urine through the glomerular filtrate This and other considerations have led these workers to postulate the "pseudosecretory" addition of hydrogen ions, arising in the tubule cells, to the tubular urine in exchange for sodium. However, establishing the specificity of this process or its dominance is a thorny problem whose proposed solutions cannot easily be checked experimentally. The ionic exchange hypothesis involving hydrogen ion and perhaps sodium ion implies metabolic transport of hydrogen insofar as it may have a U/A ratio other than 1 It is likely that hydrogen ions are generated from shifts in physiochemical equilibria as other electrolytes are transported across the tubules and that hydrogen ion regulation is an integral part of hydroxyl ion regulation

Since the product of hydrogen ion concentration and hydroxyl ion concentration is constant

$$U_{H}/A_{H}=A_{OH}/U_{OH} \qquad (116)$$

$$\log(U_{H}/A_{H})=\log U_{H}-\log A_{H} \qquad (117)$$

As an approximation

$$\log(U_{H}/A_{H})=(pH)_{A}-(pH)_{U} \qquad (118)$$

Where osmotic work, W, is proportional to $\log(U_{H}/A_{H})$ (§4 2)

$$W \propto [(pH)_{A}-(pH)_{U}] \qquad (119)$$

And similarly,

$$W \propto [(pOH)_{U}-(pOH)_{A}] \qquad (120)$$

held here that the *Cushny view remains essentially* a most powerful, accurate, and elegant expression of the urinary function of the kidney The departure itself may be referred to *the fact that Cushny was* concerned with the threshold of appearance or excretion, while the threshold of retention is adopted here. It is probably true that there occurs reabsorption into the plasma of some substances whose presence is not desirable,* through individual, somewhat independent processes Yet Cushny's concept of urine as a "secretion," even if not of a typical secreting gland, which exerts its physiological action in the process of its formation and removal, remains potentially as fruitful (if no more simplifying) for the design of physiological researches as any *theory so far devised* It remains so despite his rejection of the demonstration of tubular secretion by Marshall and Vickers[728] which *most students regard as having established this form of "negative* reabsorption "

The singular and specific phases of reabsorption of water and solutes which have been postulated by modern renal physiologists do not change greatly the complexion of Cushny's theory. The formation of terminal urine still reflects the sum of all preceding renal activities The division of tubular reabsorbate into "obligatory" and "facultative" volumes, proposed by Smith[999] and later amended[1003, 1124], has use in the study of renal dynamics but its value in elucidating urinary function *as this term is used here remains to be proved*

Wesson, Anslow, and Smith[1123, 1124] have proposed the idea that sodium, chloride, and bicarbonate are ordinarily reabsorbed *actively* in the proximal tubule, leading to the formation of a slightly hypotonic tubular urine. Across the osmotic gradient between this urine and the plasma, water is supposed to diffuse back into the plasma (passive reabsorption) so that a fluid essentially isosmotic with plasma is delivered to the distal tubule. These authors believe that water and sodium are actively but independently reabsorbed in the distal tubule by processes which are limited by maximal rates of transfer. *Relative* retention and excretion is accounted for by postulating a set of *distal Tm* values *for sodium, other electrolytes, and for water*. The actual reabsorption of the latter may be less than the maximal reabsorptive *capacity* and, *in this view, it varies* according to the influence of the

* Actually, it remains to be demonstrated that reabsorption of substances such as urea, uric acid, etc, serves *no physiological function, regardless* of how obvious the presumption. Our present "clear inferences" may be clogged with prejudice. The fact that a substance in the plasma is usually above its threshold does not signify a want of optimal conditions. Renal activity is only one element of physiological regulation.

antidiuretic hormone of the pituitary. The proposed system of tubular maxima is an elaboration of that previously assumed for substances like glucose and phenol red (§3 15) although none of the supposed tubular reabsorptive constants for water, sodium, etc has been experimentally determined As a load of sodium enters the distal tubules, depending on its being greater or less than that tubular reabsorptive constant, it is excreted freely or not The filtered load is a function of both filtration rate and plasma concentration and each of these load factors is assigned a role in the process of sodium excretion. These authors suggest that what the tubules do is reabsorb certain ions and water "*separately* and *independently*, though perhaps in such proportions that the net result is as though they reabsorbed a solution of constant composition with respect to these constituents" It may turn out, following a period of research dedicated to the determination of renal parameters, that such a set of independent systems actually exists and can account for the known properties of renal excretion, in which case a chapter in fundamental renal physiology will have been completed However, the tubular maximum hypothesis must justify itself

Even if we grant the possibility that present methods of measuring glomerular filtration rate retain absolute validity under conditions where the glomerular filtration rate is actually changing, the matter of precision in the determination of the filtration rate becomes of paramount importance in the establishment of a so-called tubular maximum reabsorptive rate How much significance can we attach to such a "constant" if a change in the alleged filtration rate of only 4 or 5 per cent (which is within the limits of experimental error) can account for an increase in the urinary excretion of sodium equal to several times the normal value, or a reduction of its excretion to zero? How can we ascertain that the altered excretion rate is not a function of altered tubular reabsorption? Or how can we tell that both glomerular and tubular functions do not change? In an attempt to prove the physiological nature of the tubular constant it is neither conclusive nor relevant to cite pathological cases in which glomerular filtration may be grossly altered

Any aberration in excretion or retention can be accounted for simply by assuming percentually minute changes in either glomerular filtration or tubular reabsorption, as a result of hormonal influences, interactions of other ions calling simultaneously for excretion, expanded or contracted circulation, etc. But the forcefulness of the tubular maximum hypothesis is then vitiated since the term "maximum" stands for little more than a conveniently adjustable variable—a deus ex

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machina Asseveration of independence and separateness of water and other excretory systems pleads for the recognition of a pattern of renal excretion which may be unverifiable. Renal topology provides a basis for alleging separateness of excretory systems but scarcely for independence There must always be a proper, if variable, ratio between tubular reabsorption of some electrolyte like sodium and tubular reabsorption of water if normal plasma concentrations are to exist, and the physiological regulation of this ratio does not argue for independence of its factors. Finally, on the basis of *histotopochemical evidence* obtained in rabbits before and after supposedly paralyzing any active tubular reabsorptive mechanism *for chloride, Ljungberg[678]* concludes the reabsorption of chloride is *passive* in the proximal and active in the distal tubules *and collecting ducts. These results are* opposed to the view of Wesson, Anslow, and Smith in its present form And Conway et al [238] *state categorically that the proximal tubule* (in the frog) is *impermeable* to sodium.

*Admittedly an oversimplification in some respects, the tubular max*imum hypothesis remains nevertheless the only unified scheme which *purports to mechanize the renal excretion of both electrolytes and* nonelectrolytes Its ability to predict as yet unknown relations in renal *excretion should test it better than its ability to account for known ones* so long as its consequences must be sought in the fringes of experi*mental error*

8.2. *Definitions* The nomenclature dealing with urine flow has *rarely* been accorded much attention, although from time to time suggested definitions of terms, or classifications for types of diuresis or *diuretics, appear It is helpful to possess a basic terminology as precise* as current theory and observation permit.

Agents, in the relation to urinary flow, can be classified as diuretic, adiuretic, or antidiuretic A diuretic agent (for example, water) is one *which brings on a diuresis* or a temporary increase in the rate of urine formation, that is, in the rate of output of water by the kidney. *Small loads of* inulin, or even of salt, may be adiuretic (at some times if not at others) in that they do not influence appreciably the rate of *urine flow*. Dehydration or pitressin may be antidiuretic in bringing about reduction of an elevated urine flow. Schmidt and Hayman[937] *observe that* diuretic agents can increase the amount of fluid leaving the blood of the kidney not only in the urine but in the lymph as well But adrenalin increases lymph flow while decreasing urine flow in the narcotized dog In some instances lymph flow is larger than urine flow although both are absolutely small

The term diuresis is often qualified as "salt diuresis," "water diuresis," "mercurial diuresis," etc in which cases reference is made to the specific diuretic agent To indicate increased renal output of particular substances, specific terms such as "chloruresis," "glycuresis," "hydruresis" are used For excretion of solute in general I propose

TABLE XX

	Urinary Fluid		
	Reduced flow	Normal flow	Increased flow
Temporary	Antidiuresis, oliguresis	Adiuresis	Diuresis
Sustained	Antipolyuria, oliguria *	Homaluria, normaluria,** eu hydrouria ***	Polyuria

	Urinary Solute		
	Reduced excretion	Normal excretion	Increased excretion
Temporary	Antilyuresis, oligolyuresis	Alyuresis	Lyuresis
Sustained	Antilyuria, oligolyuria	Homalyuria	Lyuria

The adjectival endings corresponding to and distinguishing the suffixes "-esis" and "-ia" are, respectively, "-etic" and "-ic," i e, oliguresis, oliguretic, oliguria, oliguric

* "Anuria" refers to the absence of urine formation, temporary or sustained Three types are suggested: *prerenal*, due to fall in blood pressure or impaired circulation, *renal*, as in disease, and *postrenal*, as in obstruction of the urinary passages[545]

** Veil[1090]

*** Rapoport et al [884]

the term *lyuresis* to be used for increased excretion rates, and *antilyuresis* for decreased rates Thus, where the suffix "-uresis" does not combine well with a given word stem, we may substitute forms such as "sodium lyuresis," "magnesium lyuresis," etc. In this way the confusing terminology is removed whereby "potassium diuresis" can mean either an increased urine flow following potassium intake or

an increased excretion of potassium, as after excess of cortical hormone *Antidiuresis* is defined as a temporary decrease in the rate of urine formation. While this definition is usually clear, it does not distinguish the reduction of a diuresis toward normal urine flow from the reduction of normal flow below normal. *Oliguresis* will be used to emphasize the latter action.

An important, if arbitrary, distinction in the alterations which occur in urinary flows can be made on a temporal basis Certain changes in the rate of urine formation are temporary; others are relatively sustained Thus, where *diuresis is temporary, polyuria is sustained.* Despite questions which arise in differentiating a brief polyuria from a prolonged diuresis, the separation is well taken in the interest of a more accurate nomenclature for urinary function. Table XX embodies the terminology used in this book.

Occasionally the term diuresis is used to signify an increase in urine flow of sufficient magnitude to effect an absolute dehydration of the body, a consequence of the frequent use of diuretics in clinical medicine for the purpose of removing edema. The difference between diuretic actions which bring about absolute dehydration and those which do not warrants special consideration Lyon[693] introduced the term *exogenous* diuresis to indicate that an increased urine flow merely derived from an excessive intake of fluid This was distinguished from *endogenous* diuresis in which the urine volume depended on the removal of tissue fluid Lipschitz and Hadidian[669] similarly distinguished diuretics which can or cannot drain tissue fluid, listing urea, lactamide, melamine, and salyrgan in the former group and theobromine, formoguanamine, and adenine sulfate in the latter I have called those diuretics *ecuretic* which induce an absolute dehydration of the body to a water content lower than the prediuretic period[1173] Diuretics which do not bring about absolute dehydration are called *nonecuretic* Mercurial compounds, water, sodium chloride solutions below the MIC and sodium chloride solutions above the LIC are often ecuretic (§6 5, 7 6). Sodium chloride solutions between the MIC and the LIC are nonecuretic diuretics

8.3 *The Measurement of Diuretic Activity.* In criticizing the poor criteria often employed to assess a diuretic agent, Smith[999] stated formally conditions which should be met for the demonstration of diuretic activity These included the consistent and reproducible elevation of the urine flow as determined by catheterized specimens in well

controlled experiments, from moderate, rather than very low levels; the attainment of a urine flow at least comparable to that observed after a moderate dose of water, and the persistence of such an increased urine flow for a period of at least 30 minutes Urine collections of either a few minutes or 24 hours duration were considered to have little meaning for the problem.

The caprices of the urine flow make it dangerous to draw conclusions from any but most carefully controlled experiments, but somewhat different criteria should be applied to the demonstration of a diuretic principle, that is, diuresis, depending on whether the viewpoint is pharmacological or physiological Smith's criteria serve well for the former case Physiologically, however, significant and important diuretic effects may occur in changes of urine flow from low to higher levels; comparisons with water diuresis may not be relevant; and it may not be wise to reject the possibility of establishing significant (statistically or otherwise) durations of diuresis which do not conform to arbitrary minimal or maximal periods of urine collection.

Lipschitz, Hadidian, and Kerpcsar[670] have introduced a useful bioassay for diuretics They determine the *diuretic activity* as the diuretic potency of a substance referred to that of a standard diuretic, namely, urea, the activity of which is taken equal to 1 For many substances the diuretic effects measured in a test group of rats as compared with those in a control group given saline, over a fairly large range of doses, yield an almost linear relationship between log dose (mM/kg body weight) and log effect or response This dose–effect curve of the substance under investigation and that of urea are plotted together When the two curves are parallel within the experimental error, the distance along the abscissa between the curve for urea and that for the tested substance gives the logarithm of the diuretic activity of the substance (Table XXI)

Schlosser[936] tested the effect of some diuretics in combination Using rabbits he found the smallest dose of a given substance which was appreciably diuretic and called it the "minimal diuretic quantity," D Then he found D' for another diuretic. On the assumption that $0.5D+0.5D'$ would by simple addition of effect give the same appreciable diuresis as each individual diuretic gave alone, the degree of synergism or antagonism in the combination was estimated by how the sum of the coefficients of D and D' differed from 1. In the combination $(1/8)D+(1/3)D'$, potentiation is evident where the sum of the coefficients is less than 1. Antagonism is reflected where the sum of the coefficients is greater than 1

8.4. *Classification of Diureses and Diuretics.* Pharmacologically, classification of diuretic agents, at best an arbitrary and empirical matter, carries didactic advantage. Schemes[443] embodying the terms "osmotic," "acid-forming salt," "xanthine," "mercurial," *etc.* as applied to diureses and diuretics leave much to be desired from the

TABLE XXI

Comparison of diuretic activities from the dose-action curves and from human therapeutic loses[670].

Substance	Average Single Human Dose			Rat Dose for Diuretic Action 1 5–2 5	Diuretic Activity		Ratio Rat Dose/Human Dose
					Human	Rat	
	gram	gram/kg	mM./kg	mM /kg.			
Jrea	20–40	0 3–0 6	5–10	12–25	1	1	2 5
Biuret						1.4	
odium acetate						2 0	
'otassium acetate	15–30	0.23–0 46	2 4–4 8	4–8	2 1	3 4	1.7
odium nitrate						2.9	
'otassium nitrate . .	6–13	0 13–0 20	1 3–2 0	2 5–6 0	4	3 9	2 5
.mmonium hloride . . .	10–20	0 15–0 30	2.8–5 6	4 6–8 9	2	2 7	1 6
		mg /kg.					
heobromine .	0.5–0 6	7.7–9 2	0 043–0 051	0 7–1 4	150	7.2	20
affeine . . .	0 1	1.5	0.008	0 1–0.4	625	abt 32	12–50
heophylline .	0.15–0.20	2 3–3 0	0 013–0 017	0 07–0 16	480	115	5–10
alyrgan . .		2 4	0.004–0 008	0.027	1250	abt 400	5
ismuth Na (K) tartrate	0 03–0 09	0 5–1 5	0.0017–0 005	0 025–0.075	2000–3000	220	15

physiological viewpoint. It is not difficult to bring forward instances where urine flow is only remotely colligated with urinary freezing point depressions or with urinary concentrations, for example, in glucose, sulfate, and urea diureses[962, 1177], or sodium and potassium diureses[1173]; *alkalinizing salts are often quite as effective as acid-forming* salts[132, 584, 831]; compounds more and more distantly related to the xanthines continue to show diuretic effects[671, 673]; and non-mercurial, heavy metal diuretics are well known[230, 485, 734]. It is

demonstrable, therefore, that classifications based on chemical or physical properties are not yet sufficiently discriminating, or are specious. Certain other classifications such as "water diuresis," "salt diuresis," "cold diuresis," etc are undoubtedly tenable and later discussion will adhere to a modified pharmacological scheme, using characterization by specific agent where that seems best suited.

In some ways clearance analysis has obscured rather than enlightened the classification picture because it leads us to suppose that diuretics act simply by altering the rate of glomerular filtration or tubular reabsorption of water, or both Figure 34 illustrates the only five combina-

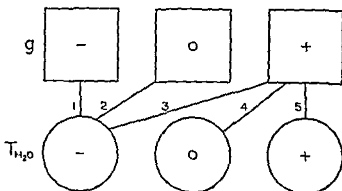


Fig 34. Five Combinations of Changes in Glomerular and Tubular Activity which Can Effect Diuresis Where g is glomerular filtration rate, T_{H_2O} is rate of tubular reabsorption of water, and −, 0, and + signs indicate "decrease," "no change," and "increase," respectively, the numbered lines connecting g and T_{H_2O} indicate the combinations of these factors which can make for increased urine flow

tions of glomerular and tubular activity which can conceivably result in diuresis according to current renal physiology Not all of these combinations are necessarily characteristic of given diuretics and some of them are common to otherwise unrelated diuretic agents. Since the magnitude of an altered tubular water reabsorption is a value calculated from an observed change in urine flow, to attribute this change in urine flow to a change, let us say, in tubular function is only as meaningful as the information that the barn is red because it is so painted, or the tautologism that drinking water increases urine flow by means of its diuretic action. The assertion that a real advance is made in establishing the magnitude of the tubular vector in urine

formation by subtracting a factual urine flow from a hypothetical glomerular filtration rate has little more than doctrinal validity.

Circulation and Diuresis

8.5. *Blood Flow and Urine Flow.* Except where renal blood flows are diminished remarkably[1086], little parallelism is found between renal blood flow, per se, and urine flow. This has been ascertained in the dog[75, 447, 1088, 1109] with and without anesthesia; in the rabbit[269]; in the rat[294]; and in man[101, 216, 219]. Urine flow does not necessarily parallel kidney volume[447].

The glomerular filtration rate as indicated by inulin clearance in dog and man tends to be relatively independent of the urine flow except in extreme oliguria[224] although this has been questioned in the case of the dog[1146]. Filtration rate varies with the degree of body hydration in infants[744], unlike adults In frogs[372] and some other animals the urine flow varies with the inulin clearance which suggests that urine flow in these species is more intimately related to glomerular activity than in others This direct relation has been affirmed[294, 579] and denied[174, 1146] for the rabbit.

A curious diuresis described by Verney[1096] results from arresting the circulation through a part of one kidney in the isolated state The remainder, "without a moment's hesitation, secretes much more rapidly than before." This may be due to associated reduction of intrarenal pressure (§4 17). Earlier experiments of Bradford[159] showed that when a dog is left with only one-quarter of its kidney weight hydruria results.

8.6. *Blood Pressure and Urine Flow* The pulse pressure appears to exert an influence upon urine flow at least in the perfused kidney such that at constant mean perfusion pressure, the urine flow as well as chloride, urea, and total nitrogen output, varies in proportion to it[424, 555]. Changes in mean perfusion pressure are accompanied by parallel changes in the rate of urine formation in dog and rabbit[322, 323, 675, 898]. Hypotension due to hemorrhage leads to a reduction of diodrast and inulin clearances as well as urine flow in dogs when the blood pressure reaches 60 to 70 mm of mercury[243]. Following blood transfusion which restores normal pressure the original urine flow may be exceeded. In traumatic shock there is a fall in urine flow where blood pressure does not fall below 80 [illegible] of mercury[576]. However, where dogs are [illegible]-tized with [illegible]; blood pressure

levels of 110 to 120 mm of mercury which are normal for conscious dogs may represent toxic depression accompanied by oliguria[242], since proper therapeutic doses of these drugs elevate blood pressure considerably and increase plasma volume In shock, when blood is

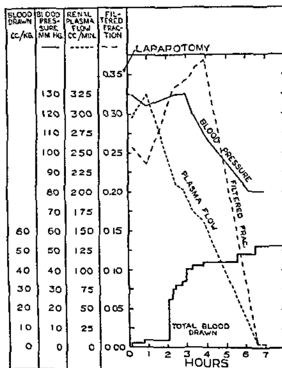


Fig 35 Effects of Gradual Blood Withdrawal in a Dog (22 6 Kg) on Blood Pressure, Total Renal Plasma Flow Measured with PAH, and the Fraction of Plasma Water Filtered in the Glomeruli. Since the blood pressure in the femoral artery was still 80 mm. of mercury in the final shutdown of the kidneys this was attributable to constriction of the renal artery or its branches. After Van Slyke [1086]

lost, the renal blood flow is decreased[1086] and there may be anuria with the blood pressure at 80 to 100 mm of mercury With blood pressure still about 80 mm. the filtration fraction is almost zero, signifying practically no residual excretory function (Fig 35). Hypertension following transfusion of blood from one dog to another does not produce diuresis[704].

Hamilton, Phillips, and Hiller[480] find that dogs with the right

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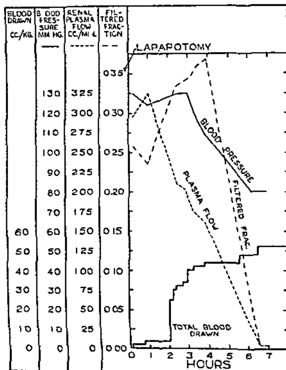


Fig. 35. Effects of Gradual Blood Withdrawal in a Dog (22.6 Kg.) on Blood Pressure, Total Renal Plasma Flow Measured with PAH, and the Fraction of Plasma Water Filtered in the Glomeruli. Since the blood pressure in the femoral artery was still 80 mm. of mercury in the final shutdown of the kidneys this was attributable to constriction of the renal artery or its branches. After Van Slyke [1086].

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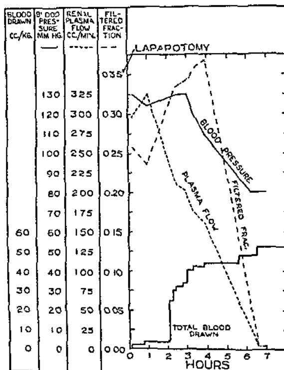


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Hamilton, Phillips, and Hiller[480] find that dogs with the right

kidney removed survive indefinitely after a two hour period in which the left renal artery is clamped, stopping flow almost completely (some flow continued to the ureter, possibly finding its way through the kidney). Some animals survived three or four hour periods After removal of the clamp renal function (measured by urea clearance) takes as long as a month to recover Occlusion of the renal vein is more rapidly injurious than occlusion of the whole pedicle[931] (§3 14, 9.13).

WATER DIURESIS

8 7. *Characteristics of Water Diuresis.* A convenient fiction has it that a man normally excretes 1440 cc of urine per day This homaluric rate, being numerically equal to the number of minutes in a day, is therefore nicely expressed as 1 cc./min *Actually significant deviations* from this precise figure abound. In a hot environment average urinary output will be less than two-thirds of this figure. Diet, extrarenal water losses, and probably other factors conspire characteristically to stamp the "normal" rate of urine flow It is observed that the ratio of the day urine volume to the night (8 00 p.m to 8 00 a m) urine volume is greater than 1:1[876, 1039] and may be as much as 4.1. The ratio 1 2·1 is given as the average for hourly rates of diurnal and nocturnal flows by Piéron[859]. *Nycturia, or excessively large nocturnal urine* volume is characteristic of certain diseased conditions. Toward the end of pregnancy the ratio of day urine to night urine decreases and may fall below unity[1054] Normal urine flow includes periodic diureses and oligureses brought on by changes of intake and of metabolism. *In diverse mammalian species*, the homaluric water output is grossly related to body weight by the equation

$$u = 0\ 000106\ B^{0\ 82} \qquad (121)$$

where u is urinary flow in cc /min and B is body weight in grams[16].

Water taken by mouth, by rectum, by vein (fortified osmotically with 5 per cent glucose)* and otherwise parenterally, although not ordinarily subcutaneously, leads to diuresis[16, 249, 521, 812]. The urine, when flowing rapidly, is dilute, having a low specific gravity and a small *freezing point depression* (§4.4, 4 7) Water in the digestive tract is

* In man the maximal injection rate of intravenous glucose solution which will not lead to frank glycosuria is of the order of 11 8 cc /min. of 5 per cent glucose (to the extent of 1 liter), or 0 5 g. glucose/kg./hr [680] In dogs and rabbits this rate is given as 0.85 g /kg /hr [923] Nonglycosuric loads of intravenous "isotonic" glucose (5 4 per cent) behave diuretically, essentially the same as equal loads of water taken orally.

said to linger a shorter time, the nearer the temperature of the water to body temperature. Also, there may be a greater and sooner diuresis with water at 40° C compared with that of water at 10° C.[83] The

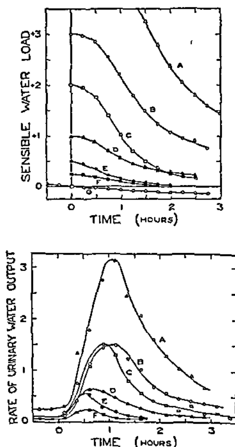


Fig 36. Upper: Water Tolerance Curves in the Dog showing the course of sensible water loads (per cent of body weight per hour) after water is given by stomach in a single dose Sensible load is total ingesta minus urine collected.
Lower: Water Diuresis Curves showing rate of urinary water output (per cent of body weight per hour) in relation to time after a single dose of water is given by stomach tube. Same tests as in upper figure. After Adolph [16]

diuretic response to a dose of water (Fig 36) is characterized by a definite delay or latent period (§8 37, 10 10) lasting from 18 to 42 minutes, a rate of water excretion rising rapidly to a peak, a short

duration of excessive excretion, the elimination of an amount of water approximately equal to the quantity of water load, and an inhibition following administration of the antidiuretic hormone of the posterior pituitary. In rats, repeated water diuresis results in the diuresis becoming characterized by less delay in onset, greater rates of output, and increased resistance to water intoxication[23, 660]. After partial nephrectomy the remaining renal tissue undergoes no more hypertrophy with the stimulus of rapid water turnover than without it

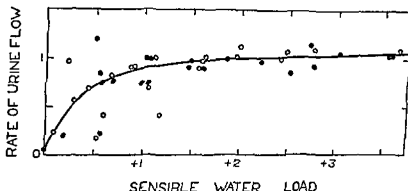


Fig. 37. Rate of Urine Flow in Man (Per Cent of Body Weight Per Hour) in Relation to Sensible Water Load (Per Cent of Body Weight). Three individuals in stationary state, 21 tests Water was ingested at one quarter hour intervals, usually in 16 portions but varying from 8 to 16. Black dots, maximal urine flow in any one-quarter hour period before ingestions ceased; white dots, maximal urine flow (and coincident load) in any subsequent one quarter hour period After Adolph [16]

The latent period for water diuresis is only relatively unique Many other diuretics do not show so long a delay before an appreciable increase in urinary output is effected; still others show a longer delay. A graded series of latent periods characterizing different lyuretic and specific diuretics could probably be arranged.

The time in hours, t, required to complete the diuretic response to water is related to the water load, L_{H_2O} (in per cent of body weight) by the equation of Adolph[16]

$$t=1.3+L_{H_2O} \qquad (122)$$

Hevesy and Hofer[539] calculate from observations on the disappearance of ingested heavy water, that in hot summer weather a water

molecule spends an average time of 13 days in the body The half-life of a load of heavy water is 9 days (thus, 13=9/ln 2).

The rate of urine formation is often proportional to the load of water (Fig 37) in the blood and tissues at any moment but beyond certain limits of load the urine flow falls off[476, 916, 1171]. It is difficult to sustain urine flows in excess of 1000 cc./hr even with constant water intake The quantity of urine collected in a diuresis following a unit

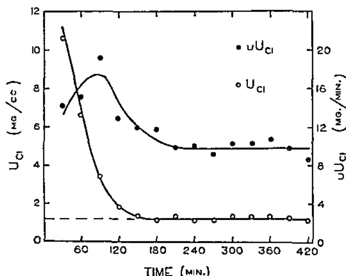


Fig 38. Urinary Chloride Concentration (U_{Cl}) and Rate of Excretion of Chloride (uU_{Cl}) Varying with Time during Steady Ingestion of Water (70 cc /10 min) in Man. Urinary chloride concentration reaches a minimum of 1 2 mg /cc by the third hour After Wolf [1171]

load of water is approximately proportional to the logarithm of the time[1057].* Thirst, per se, as induced by atropine does not change the course of water diuresis[18, 356] although large doses of this drug inhibit the excretion of water, sodium, and chloride[633]. Water diuresis does not increase appreciably the output of sodium[258], potassium[818, 1173], or chloride[318, 718] and may decrease it where the

* Quantitative relations between urine flow, time, and water load were put to practical use in the Sioux "alarm clock"[566] A Sioux warrior wanting to be awakened early to go on the war trail simply drank a lot of water before he went to bed. The earlier he was to be awakened by this primitive alarm clock, the more water he drank.

period of diuresis is short. In prolonged water diuresis (at least 7 hours) the rate of excretion of chloride may fall and become rather constant after an initial increase[818, 1171]. This phenomenon has been treated in connection with the absolute dehydrating action of continuously administered water (§6 5, Fig. 38).

The effects of diuresis on the elimination of solutes is often complex. For example, there are conflicting findings on the excretion of phosphate. It is said to be unaffected[141], increased[55], or decreased[1176] with water diuresis. Decreases and increases are also found in sucrose or glucose (50 per cent solution) diuresis[141, 591]. Several factors other than those strictly concerned with experimental technique enter into results of this sort. First, the load of solute in the animal at the beginning of an experiment may be positive, zero, or negative. Where it is positive it can be expected that some lyuresis will occur initially, followed by antilyuresis. Where the load is zero or negative, we may obtain essentially only an oligolyuresis Second, there is a temporal aspect in that loads change from positive to negative (for example a threshold substance falls below its threshold concentration), from zero to negative, or from negative to more negative, each change making for characteristic excretory patterns. Third, the height of the threshold of the substance in question may importantly influence the result. Other things being equal, low threshold substances tend less to reduce their excretion rates sharply than high threshold ones Fourth, it may be expected that loads of substances intimately colligated to the one in question may act critically in determining the excretory pattern[829]. According to Ogden and Tripp[827] water diuresis may actually lead to an increase in the production of a substance such as urea, as well as to an augmentation in its rate of excretion[52, 787].

The phenomenon of augmentation of solute excretion with increase of urine flow[959, 961] is presently explained with facility With any given glomerular filtration rate, a given load of solute is presented to the tubules per unit time. In diuresis we suppose that the rate of tubular reabsorption of water is smaller than in adiuresis, the result of which is (*1*) to decrease the concentration gradient of the solute between tubular urine and plasma and thus to decrease its rate of reabsorption, and (*2*) to reduce the time of contact of the solute with the tubular wall by virtue of the more rapid movement of luminal fluid, again favoring lesser reabsorption than in adiuresis. Presumably these hypotheses apply with more force to those substances which are passively rather than actively reabsorbed, since the excretion of the latter can be remarkably reduced regardless of the magnitude of the urine flow, under appropriate conditions

8 8. *Diet.* On a low salt diet dogs which have undergone marked chloruresis and ecuresis through previous treatment with solutions of 50 per cent sucrose may be maintained with a serum total base and chloride level 15 to 25 mEq /l below normal[552]. Although these animals seem normal they do not show a normal water diuresis, it being

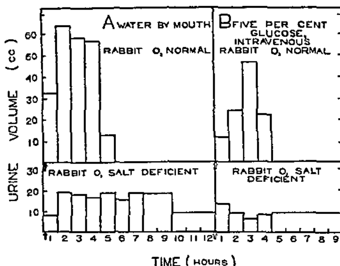


Fig 39 The Inhibiting Effect of Salt Deficiency upon the Production of a Water Diuresis Black arrows indicate midperiod of water administration in 2 doses, 100 cc. and 70 cc White arrows indicate time of administration of 100 cc of 5 per cent glucose After Wilkinson and McCance [1143] In *A*, salt deficient rabbit had a blood urea of 154 mg per cent, in *B*, salt deficient rabbit had a blood urea of 84 mg per cent The azotemia in salt deficiency may reflect generally depressed renal function although it is not fully understood [172] Salt deficiency in adrenalectomized dogs is correlated with reduced glomerular filtration [492]

either absent, less than one-third normal, or delayed one and one-half hours or more and accompanied by a fall in electrolyte concentration in the serum If animals are allowed to drink ad libitum most of the characteristic weight loss is recovered with a lowering of serum electrolyte Water diuresis in man is less than normal in mineral starved and in salt enriched subjects[59]. In dehydration of the Dd type (§6 2) water intake results in diuresis even though it may not be so marked as in the normal[521], a fact which is not explained by but is consistent with the observation that plain water intake cannot relieve for long absolute dehydration

When diet is standardized the output of water is closely dependent on the magnitude of the salt intake[96, 743, 752, 1040, 1042, 1044] in normals, dehydrated individuals, and those with diabetes insipidus Gamble[397] reports a so-called "sodium sparing" effect of dietary glucose which seems to be connected with the ability of glucose to reduce the water exchange in man. The "protein sparing" action of glucose is also related to its ability to reduce the water requirement since the excretion of nitrogenous material obligates urine volume somewhat after the manner of salt In dogs, after eating meat, there is a diuresis[435] and urine volume is invariably increased with a higher daily metabolism of protein[275]. The pattern of food ingestion may dictate the pattern of water ingestion[909] Dogs deprived of food and water for eight days show no water diuresis in response to water increment, if they have been allowed water ad libitum during food deprivation they show impaired water diuresis[16]. Hypoproteinemic rats show delayed water diuresis despite the fact that administered water may actually be absorbed from the gut more rapidly than normal[293]. In fasting there is often a decreased water intake and some degree of oliguria although this effect need not be marked and there may be an initial diuresis of uncertain origin[1148] with an increased negative water balance It is reported for a single subject that in prolonged fasting the average night urine volume was somewhat higher than the average day urine volume[99].

LYURETIC DIURESIS

8.9. *"Osmotic" or "Tubule" Diuresis. Permeation* It has long been suspected that diuretics such as salts and xanthines differ in their actions on the tubules[1011] Cushny[266, 268] attempted to generalize the behavior of the former by considering a "permeation factor." If there were present in the plasma and then in the glomerular filtrate any solute which could not permeate into the epithelium of the tubules, this was supposed to retard the absorption of the fluid in which it was dissolved and thus increase the urine flow. Cushny called this *tubule diuresis* and it is commonly referred to as *osmotic diuresis* He recognized clearly, as did others[10, 21, 383], that tubule diuresis becomes a complex matter when a dilution factor, arising from the increment of fluid (if the diuretic is given in solution) in the plasma, is also present ("dilution diuresis")

The permeation factor itself shows little correlation with diuresis Sodium and chloride are reabsorbed in large quantities yet the diuretic effect of saline solutions of different strengths (Fig. 29) has no direct

relation to the urinary excretion of these ions (Fig 24) und physiological conditions Perhaps the permeation factor must be qua fied in terms of the effective osmotic pressure of the solute within t tubules by including the elements of permeation and of solute concen tration. Studies of the comparative diuretic effects of saline solution of various kinds, of urea, and of glucose[472, 799, 1014, 1177], how ever, do not permit us to draw clear relationships between diuresis and even a qualified permeation factor

With solutions of glucose, how shall we distinguish the diuretic effect of the glucose from that of the water? It is often stated that glycuresis is essential to a glucose diuresis but this has not been thoroughly investigated and Starling[1024] showed that diuresis following 30 cc of 30 per cent dextrose ceases long before glycuresis ends. Glycuresis may be necessary but insufficient to bring about glucose diuresis Similarly, Arden[46] noted how salt diuresis falls off before all of a salt load has been removed He suspected that the kidney might be responding to impulses from some region stimulated by excess salt Shannon[961, 962] has obtained urine flows in the dog, following infusions of glucose, sulfate, and urea as high as 50 cc/min, in which the diuresis did not seem to be limited osmotically. During glucose diuresis of the type he used, the glucose concentration in the urine is invariably below 5 per cent (the urine was hypotonic with a freezing point depression (§4 4) of 0 517° C), the concentration of other constituents is negligible, and it is difficult to understand how the diuresis could be due to the osmotic pressure of the fully formed urine An attempt was made to explain this phenomenon by the assumption that an unabsorbed, osmotically active constituent in the glomerular filtrate (glucose) blocks an isotonic (obligatory) reabsorption of water in the proximal tubule, whereupon fluid is delivered to the distal segments too rapidly for the reabsorptive system in this part to effect further concentration

Most writers have been ready to relegate urea to the "osmotic" diuretic category, in spite of the fact that its permeation factor is so great (and thus its effective osmotic pressure is so low) for most cell membranes Even granting a special, low permeability of the tubular wall to urea, we may question whether this substance is otherwise inert Lipschitz[668, 669] has presented evidence that urea is only one representative of a class of xanthinoid diuretics containing the N—C—N group which has more or less specific diuretic effects (§8 19)

In salt diuresis the osmotic pressure of the urine may be about the same as normally[382], or less[536, 743, 752, 886]. Administration of sodium chloride solutions of increasing osmotic pressure (for example, from 0 to 350 mEq/l) does not generate correspondingly increasing

diuretic effects[1173] (Fig. 29). Potassium *chloride solutions (for* example, from 0 to 100 mEq./l.), however, are all strongly, almost equally diuretic Isotonic sodium sulfate solutions given intravenously are more diuretic than those of *isotonic sodium chloride[703] and* actually behave in this respect like plain water[1177]. Thus, specific action of ionic combinations stands clearly apart from osmotic phenomena.

These and other[952] serious defects in the concept of "osmotic diuresis" led the author[1173] to suggest that some diuretic actions *were more properly referable to the LIC of the solutes concerned,* as with urea or sodium chloride. In its simplest form, for no-threshold substances, the steady state equation (84), $uU = \imath I$, indicates that when *U is at the LIC (that is, esentially constant), then u (reflecting the* diuretic effect) is proportional to $\imath$ or to $\imath I$, or, therefore, to solute load Solutes which were thought to influence urine flow in this way (sodium chloride, urea, sodium *sulfate) were called "isorrheic diuretics" Since* the LIC and the MUC are often different values, the significance of osmotic pressure for isorrheic diuresis becomes conjectural. Isorrheic diuresis is not *clearly an entity and like so many other alleged types* of diuresis it too may be fictive

Isorrheic diuresis may be some function of both the threshold and the *LIC as seen from the steady state equations*

$$\frac{u}{\imath} = \frac{I - A_T}{U - A_T} \tag{95}$$

and

$$u = \frac{\imath I - i A_T}{U - A_T} \tag{123}$$

Where i is very small and $\imath I$ is some large, constant (K) value (as where salt is taken with minimal volume of water), $\imath A_T$ becomes negligible *and U attains or exceeds the LIC Thus*

$$u = \frac{\imath I}{U_{LIC} - A_T} = \frac{K}{U_{LIC} - A_T} \tag{124}$$

And for no-threshold substances for which $A_T = 0$,

$$u = \frac{\imath I}{U_{LIC}} = \frac{K}{U_{LIC}} \tag{125}$$

The fact that there is no theoretical justification for equations (95) and (124) where the LIC is exceeded (§7 8) poses the question whether substances which ordinarily have thresholds lose them and behave as

no-threshold substances under conditions in which normal plasma concentration cannot be regulated.

To avoid postulating a mechanism of solute diuresis at this time it is proposed that an increment in the rate of urine flow which is traceable to an increment of excreted solute be called tentatively *lyuretic diuresis*, a term noncommittal as to mechanism yet sufficiently descriptive for most purposes This definition requires qualifications First, it is observed that salt and glucose diuresis fall off more quickly than loads of these substances are removed from the body[46, 286, 1024], a fact which does not support (although it may be consistent with) the idea of simple convection of excess solute from the body in a medium of obligated water[950, 1170, 1177]. Second, mercurial diuresis is to some degree also proportional to the excretion of solute (mercury, itself, sodium, etc) and is only excluded from the lyuretic diureses because it is presently expedient to consider it separately. Presumably as our understanding of diuretic actions increases, more scientific classification of diuretics will become possible Here, lyuretic diuresis, by exclusion, refers to those diureses not falling into classes otherwise defined Lyuretic diureses are thus grossly distinguished from relatively specific diureses such as those of mercury, xanthinoids, or water They may be brought about by both threshold and no-threshold substances and their magnitudes depend on the amount of solute finding its way into the urine[886] rather than on the clearance or plasma level of the lyuresed material.

In those instances where the limiting osmotic pressure of the urine due to all dissolved substances appears to determine urine flow[536], the velocity constants of the lyuresed solute is of importance[1170]. Where urea has a given velocity constant of excretion, increase of the load in the body implies proportionally increased excretion rate Where an LIC exists the urine flow takes up whatever rate is consistent with the colligated excretion rate, load, and velocity constant of the solute in question The fundamental basis of lyuretic diuresis remains obscure The advantage of the term "lyuretic" over "osmotic" with respect to diuresis lies in the fact that urine flow is a well known function of excessive solute excretion, whereas it is not established that it is a function of urinary osmotic pressure in any simple form. I believe the osmotic factor is best regarded for the present as merely one element in a complex picture which invites clarification No one has yet proved that urine flow is determined by osmotic limitations rather than that osmotic limitations are determined by *urine flow*

An idealized osmotic factor in diuresis might be illustrated as follows. Suppose a freely filterable, unreabsorbed, unsecreted, "osmotically

The premise that terminal or bladder urine will be hypertonic in an "osmotic" diuresis, that is, that there need be a *positive osmotic concentration gradient*, $(U-A)$, is challenged directly by Wesson, Anslow, and Smith[1123, 1124] (§8 1). They hold that the osmotic action of filtered solutes interferes with a *passive* reabsorption of water in the proximal tubules thus causing more isotonic fluid to pour into the distal tubules *At this latter site, the limited reabsorptive* capacity (active) for water, $(Tm^d)_{H_2O}$, is exceeded and a urine, tending to the isotonic as its rate of formation increases, is found. This tubular maximum hypothesis of osmotic diuresis should be useful if more direct evidence can be brought forward to establish it as other than an ingenious scheme to rationalize only restricted facts of lyuretic diuresis.

How to decide whether water reabsorption in the proximal tubule is active or passive is not so obvious If we accept the premise of active reabsorption of sodium and concomitant reabsorption of water, how do we know whether the latter is a passive, osmotic consequence or an active metabolic simultaneity, or a combination of both—and does it make any difference for the facts on hand? With mannitol diuresis it is found that some considerable quantity of sodium always remains in the urine in lower concentration than in plasma, at high urine flows, and that $(A-U)$ rarely exceeds 60 to 90 mEq/l. This has been considered by Wesson et al a limiting gradient in the proximal tubule beyond which the tubule cells could not go With passive, osmotic water reabsorption in mind, one can state that more than the ordinary amount of water flows through the proximal tubule in a unit time, with the osmotically active mannitol and remaining sodium More than the ordinary amount of these flows into the distal tubule, flooding its assumed $(Tm^d)_{H_2O}$ and $(Tm^d)_{Na}$, and more than the ordinary amount of water and sodium are excreted finally It is of interest to note, however, that mannitol or glucose given during water diuresis may increase sodium excretion with no change or even a decrease in urine flow[892].

Consider the case of sodium sulfate We might suppose that, like mannitol, large quantities of sulfate remain unreabsorbed in the proximal tubule[950]. By the principle of electroneutrality (§7.17) a block of sodium sulfate would similarly remain When we examine the urine in sodium sulfate diuresis we find often that there is no excess sodium in the urine which is not neutralized by sulfate, that is the $(A-U)_{Na}$ (for Na in excess of SO_4) gradient is perhaps 140 mEq/l. [1177] This behavior, and that of urea[796], differs sufficiently from that of mannitol to raise the question of whether this gradient is critical We might simply state that practically all excess sodium (that approximately electroneutralized by chloride, bicarbonate, phos-

phate, etc.) is reabsorbed actively; that water is reabsorbed perhaps passively in part, but finally actively, until a critical $(U-A)_{Na_2SO_4}$ —or a critical gradient between tubular urine and the interior fluid of tubular cells (§4 3)—was reached whereupon all remaining filtered water appeared in the urine with sodium sulfate at its LIC (Table XVI) In the case of mannitol which appears to be able to replace sodium in the plasma (§7 16), we could state that mannitol and sodium share a common LIC

At the present time a return to the older idea of active water reabsorption is not precluded by any particular findings Neither is it necessary to invoke a separation of proximal and distal mechanisms of water reabsorption on a basis of the activity of the pituitary antidiuretic hormone since the endogenous hormone does not apparently modify the course of sodium sulfate-water diuresis in the normal animal The excretion of other ions such as potassium, calcium, magnesium, etc [1177] is augmented during sodium sulfate diuresis and it would seem that this fact, and whatever "specific" influences sodium sulfate has on the tubules in this regard, concern intimately the nature of the diuresis produced The attempt to account for lyuretic diuresis in terms of any one ion or pair of ions is probably, like its counterpart in slippery explanations of edema, doomed to fail

In fine, there are numerous questions which must receive satisfactory answers before a comprehensive mechanism for lyuretic diuresis can be considered established (if, indeed, the classification "lyuretic" is a proper entity) At least let us ask how it is that diuretics such as mannitol[892], urea[885], and sodium sulfate[950, 1177] have different effects on salt output and plasma concentrations of sodium and chloride, if they are all simply "osmotic" diuretics? How can we base the mechanism for active reabsorption of water on the antidiuretic hormone of the pituitary when hypertonic urine can be formed in the absence of this hormone, when removal of the adrenal cortex together with the source of this pituitary hormone prevents the development of diabetes insipidus (§10 16), and when the maintenance of definite u/i ratios in steady state water intakes clearly attests to the regulation of water output in the absence of antidiuretic hormone at widely varying water loads? How are we to quantitate the comparative "osmotic" diuretic effects of ions like sodium, chloride, potassium, etc if these are to variable degrees reabsorbed and altered in their plasma concentrations? How is it that within wide limits the urine in salt diuresis tends not to have an isotonic but rather a hypertonic LIC[433, 1170]? And when is an "osmotic diuretic" not an "osmotic" diuretic? These are not captious questions.

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Anslow[1123] that sodium, chloride, and water are not reabsorbed in a constant ratio as diuresis increases in magnitude, and this was taken as evidence of the independence of the reabsorptive processes underlying their excretion To conclude the independence of sodium and water excretion on the basis of such experiments which apply stresses to the kidney so severe as to prevent that organ from executing its normal urinary function (including maintenance of sodium concentration in the plasma) is physiologically meaningless When solutions stronger than the LIC of sodium chloride are steadily infused an observer may conclude equally that because water is being lost ecuretically and salt is being retained in ever increasing quantities, the two excretions are controlled by "independent" mechanisms, and this might have a degree of validity. But reasoning from these metaphysiological facts alone cannot divulge the nature of normal renal function It is not much more strange to ask for an interpretation of the facts of normal body temperature regulation from the response of a dog placed in boiling water

[illegible]

sulfate, and urea have marked diuretic effect. Although the salts excreted by the kidney seem to have the most effect, equimolecular solutions of chloride of a series of cations (lithium, sodium, potassium, and rubidium) produce a progressively increasing diuresis with increase of molecular weight, while solutions of chloride of magnesium, calcium, strontium, and mercury give a progessively decreasing diuresis with increase of molecular weight Here again specific ionic action appears to play a unique role

8 10 *Sugar, Mannitol, and Urea Diuresis* Strong solutions of glucose, sucrose, and lactose are powerfully diuretic but lead to functional renal impairment and to histological alterations in the tubules such as foamy swelling (hydropic degeneration)[43, 526–528, 633, 661] If these diuretic agents are not used too frequently, structural and functional changes are reversible and not considered harmful When 50 per cent sucrose is injected into rabbits the urinary concentration of sugar does not exceed 10 per cent Sugar diuretics are extremely ecuretic and lyuretic[552, 581], resembling mannitol[1123, 1124], but they are unlike urea which does not markedly increase salt output[285, 366, 885, 952, 1078]. However, high urea diuresis has been observed to increase the excretion of salt when the latter is loaded in the body along with urea[796] Urea diuresis during the action of excessive pituitrin is also salt lyuretic[1078]. Administered during water diuresis, neither

urea nor glucose bring about marked sodium lyuresis[258] although some increased sodium excretion is reported[892]. Phosphate excretion is depressed by mannitol and accelerated by glucose[952].

§ 11. *Salt diuresis* The temporary increase in urine flow referable to the introduction into the blood of saline solutes[10] and to their urinary excretion is known as salt diuresis (Fig. 40) The term has been used erroneously to signify salt lyuresis, that is, an increased urinary excretion of salt

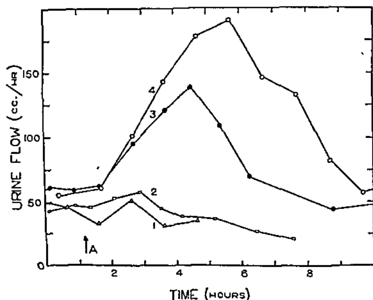


Fig 40 Salt Diuresis in Man The effects on urine flow following the ingestion at *A* of varying amounts of sodium chloride. (*1*) 3 g, (*2*) 8 g; (*3*) 17 g, (*4*) 30 g After Adolph [10]

Hypertonic salt solution injected subcutaneously produces a diuresis which is delayed more than that following intravenous solution[259], a latency which is traceable not only to the absorption time for the bulk of injected fluid, but also to the fact that hypertonic solutions placed in regions which restrict their free escape are of low fugacity and initiate a movement of water from other parts of the body into the region they occupy. It is not certain what factors determine the latent period of diuresis following injections of salt solutions. Such

a latent period may be quite variable depending on the nature, concentration, and quantity of salt injected. With some solutions diuresis may proceed almost from the moment of injection[472]. The greatest urine flow following administration of hypertonic sodium chloride does not necessarily coincide with the greatest plasma concentration of chloride[286].

The salt diureses which apparently have some roots in osmotic or isorrheic phenomena have been discussed (§8.9 ff.). These include diureses from hypertonic solutions of sodium chloride, bicarbonate, and sulfate[886, 943, 1173]. Other salt diureses (potassium chloride, bicarbonate) are less well correlated with osmotic or isorrheic effects and reflect more strikingly "specific" tubular effects of the loaded solutes.

8.12. *Potassium Diuresis. Ringer's Solution.* The diuretic action of potassium salts was first reported by Wilks and Taylor[1144]. Blum[132] and particularly Keith and Binger[584] studied the clinical efficacy of these salts including the bicarbonate, chloride, nitrate, acetate, and citrate. The latter investigators showed for their experimental conditions (salts given as 0.13 to 0.2 g./kg., in 25 per cent solution) that the nitrate and then the chloride were the most effective, then bicarbonate, acetate, and citrate. Peters[840] raised the question as to whether potassium had any specific diuretic influence or whether diuresis after administration of potassium or any indifferent ion was not referable simply to restriction of sodium chloride. Probably this is not the case[1173]. It is true that certain dilute solutions of potassium chloride, for example, cannot easily be distinguished from water so far as their effects on the load of water remaining after a short time are concerned (Fig. 32). But potassium chloride solutions have a greater lyuretic effect in removing sodium and some bicarbonate from the body than does water, and in longer periods of adjustment specific ecuretic effects of potassium chloride may be demonstrable as is the case more promptly with more concentrated solutions.

By virtue of the fact that diureses from water and from certain solutions of potassium are similar we cannot attribute the effect of salts like potassium, when given in solution, to any definable osmotic influence. It is difficult to avoid the simple if inadequate view that potassium salts call forth renal responses specific for any given compound which is loaded on the body. These responses in turn may depend upon the state of surfeit or paucity of all other substances calling for renal excretion.

It is convenient to think of diuretic salt solutions as composed of two elements, water and salt, giving rise respectively to water diuresis and lyuretic diuresis A graded series of mingled influences is found as solutions of increasing concentration are loaded on the body and it is not always easy to tell where each is particularly effective or ineffective. Where an LIC exists, as with urea, we can tell fairly closely at which concentration a specific ecuretic effect of the solute begins, but a graded series of diuretic influences due to urea is still perceptible (Fig 30) In the case of sodium chloride solutions (Figs 26, 29) the diuretic influences of the components are so interrelated that in short time periods it is as though there were an inhibitory effect of salt on water diuresis, most marked with solutions in the concentration range 100 to 200 mEq/l (§9 12). Nevertheless these effects are still diuretic ones and not antidiuretic since with administered solutions of any concentration urine flow is increased.

Ringer's solution has variously been reported more diuretic than normal saline[231] or not significantly different[670] Pfeiffer, Roby, and Smith[846] state that the addition to 0.45 per cent sodium chloride of calcium, potassium, or magnesium to give the same concentrations they have in the blood, renders the saline more diuretic when taken orally Calcium is said to be the least effective, magnesium the most, and potassium of intermediate potentiation More data, however, will probably be required before ionic influences on saline diuresis become clear.

Salt solutions approximating human serum in composition are said to be more palatable than equivalent sodium chloride solutions[872]

8 13 *Acidifying and Alkalinizing Salts. Intravenous Calcium* Ammonium chloride, sulfate, and nitrate, and calcium chloride (orally) are so-called "acid-forming" salts which bring about diuretic activity[398, 592]. The effect of these ammonium salts, after metabolic conversion of the cation to urea is similar to the effect of a load of hydrochloric, sulfuric, or nitric acid With calcium chloride there is a failure of absorption of calcium from the gut (which eliminates it as insoluble carbonate, phosphate, and soap) and an effective absorption of hydrochloric acid, whereupon a similar acidifying action results *There is a decrease in plasma bicarbonate, an increase in plasma concentration of the anion administered, a decrease at times in the plasma concentration of sodium, a general lyuresis (Fig. 32), and an ecuresis which in edema may be effective in removing considerable quantities*

in those with edema[583], and in those with diabetes insipidus[621] *Chloride* concentration in the urine rises with the peak of diuresis to levels above that in the plasma[391]. The chloruresis, which is roughly proportional to the quantity of mercurial given[912], is often a better criterion of the renal action of these diuretics than the diuresis, and to some extent they are independent. In dehydrated dogs there is frequently a great chloruresis with no diuresis following administration of organic mercury compounds. Mercurial diuresis in man usually begins in the first half hour after intravenous injection and becomes maximal in the second hour, time relations which do not vary with the size of the diuresis[350]. Whereas in normal subjects diuresis lasts only during the excretion of the mercury, in those with edema the diuresis is prolonged, reaching a peak in 6 to 8 hours and often continuing into the next day[1015]. This effect, sometimes attributed to a so-called "mobilization" of edema fluid which is supposedly out of renal contact before the diuretic is given, is actually of unknown origin (§5 4).

It is not known precisely how mercurial diuretics act. They are said to hinder the tubular reabsorption of water, sodium, and chloride[999] and may increase the excretion of potassium sufficiently that its clearance exceeds that of creatinine[103] This suggests that potassium can actually be secreted by the tubules, providing that the glomerular filtration rate does not exceed the creatinine clearance under these experimental conditions (§3 13). Since many diuretics appear to act in man and dog by hindering directly or indirectly the tubular reabsorption of water, this fact is of little special value To suggest that mercury is "irritant" to the tubules is likewise nondiscriminating; neither can we be sure that its effects represent an early stage in toxic action[443] particularly in view of the increased concentration ratio for chloride which it brings about Furthermore, the curious synergisms and antagonisms which exist between mercury compounds and other substances do not favor any such simple view Beyond what can be said of the nephrodynamics of mercurial diuresis in terms of inulin clearance, the underlying mechanism of action and the patterns of solute and water excretion which it makes are not well known.

8 16. *Ecuresis and Lyuresis* Mercurial diuretics are particularly ecuretic in the presence of cardiac edema if other conditions are conducive to their action[256]. Blumgart et al [138, 139, 140] found that the greater the edema, the greater the effectiveness of these drugs in bringing on absolute dehydration. They cause an increased excretion of sodium, chloride, potassium, and calcium with no significant change

in the metabolism of phosphate, sulfate, ammonia, total nitrogen, or urea[391] The ratio between the lyuresed solutes and the ecuresed water is approximately equal to or somewhat greater than their concentrations in body fluids[140]. Although a fall in plasma chloride may occur following the elimination of a urine more concentrated in chloride than the plasma, the change is not always clear. With the onset of mercurial diuresis there is a diminution in plasma volume proportional to the magnitude of the diuresis[351]. In consequence of the dechloridization of the body which occurs, associated with a cellular hydration at the expense of extracellular fluid as the chloride concentration of the latter falls (hyposalemia), drinking is augmented less than the diuresis, in per cent of intake[620]. Normal human subjects may show some thirst after mercurial diuresis, the explanation of which has not been attended carefully. This phenomenon is less common in edematous patients.

8 17 *Synergism and Antagonism* Keith, Barrier, and Whelan[583] first indicated that a diuretic synergism existed between ammonium chloride and mercurial diuretics Combined in nephritic edema, these dissimilar diuretics produced clear ecuretic responses whereas each alone was relatively ineffective An additive effect was likewise demonstrated between mercurials and acidifying salts (ammonium nitrate and ammonium chloride) by Jacobs and Keith[564] and both types of synergism were subsequently confirmed[123, 366, 589, 590]

The nature of these synergisms with mercurial diuretics is poorly understood When plasma chloride is low, mercurials do not have potent diuretic properties[350] When there is a tendency to alkalosis, or where alkalinizing salts are given, mercurials similarly exhibit little diuretic activity[344, 348, 349, 924] Keith[582] has stated that two factors aid mercurial diuresis, namely, proper (normal or elevated) plasma chloride level, and a positive systemic acid balance A diuresis resulting from synergism between ammonium nitrate and an organic mercurial may lag after a time, as the plasma chloride falls, but it is readily restored by substituting ammonium chloride for the nitrate However, Blumgart et al [139] note a patient in which the plasma chloride was high, bicarbonate low, and sodium low There was little diuretic response to mercury Sodium bicarbonate was given whereupon sodium was retained with no gain in weight When acid-base balance was reached spontaneous diuresis occurred These results were taken to indicate that the sodium level is significant in mercurial diuresis (§6 3).

The diuretic effect of mercury cannot strictly be referred to salt lyuresis since pituitrin can inhibit the diuresis without reducing, or even with increasing, the salt output (as it may do in the absence of mercury). Also, mercury administered during water diuresis augments the salt output but does not greatly affect the urine output[258]. Cortical hormone polyuria (§10 15) occurring with salt retention also evidences a high degree of freedom between urinary excretion of water and salt. This need not signify independent handling of these materials but rather an alteration at some new level of water balance of either the ionic thresholds, control of fluid intake, both, or perhaps other factors

Xanthine and Xanthinoid Diureses

8 18. The diuretic effects of xanthine derivatives were first established by von Schroeder[947, 948] who studied caffeine, theobromine, and related substances. The action of caffeine is complicated by its circulatory and central nervous system effects, but like many other diuretics, it (and other xanthines) appears to act primarily by hindering the tubular reabsorption of water Glomerular or circulatory changes in the kidney are not necessary for its action[999]. Dogs and frogs are not so responsive to caffeine diuresis as rabbit and man[268, 781]; cats in general do not respond well to diuretics

8.19. *Synergism and Antagonism.* The action of certain members *of the caffeine group* (caffeine, theobromine, theocin) in dogs in water balance is to decrease daily urine output, that is, they are oliguretic, according to Wallace and Pellini[1112] The diuretic action appears [illegible] there is excessive water in the body. Rabbits on a dry diet show

[illegible] (caffeine, theophylline) potentiate water diuresis Eggleton[318] finds that tea diuresis averaged 1.55 times as great as water diuresis when comparison was made between [illegible] [926]

ate the action of caffeine (§8.3) while caffeine sodium salicylate [illegible] *theocin work together to give only simple addition* of their diuretic effects Theophylline diuresis is increased by pituitrin[1078]; that of caffeine is little affected[671].

Intraperitoneal distilled water inhibits the specific action of theophylline ethylenediamine[264] in a manner which depends upon the

deviation of chloride and other electrolytes from the plasma into the fluid bulk in the peritoneal cavity. If 2.5 per cent sodium chloride is given while water is in the cavity, the diuresis is not inhibited. Intraperitoneal isotonic glucose, like distilled water given this way, can also cause serum to become hypotonic with consequent cell hydration and oliguresis[281].

Xanthines have a chloruretic effect, the chloride in the urine being approximately the same as in an equivalent amount of body fluid[140]. Theophylline brings on potassium lyuresis in the rabbit[818]. Administered during water diuresis in man, it increases the excretion of sodium with little change in urine flow[258]. If given with isotonic saline, urinary flow is greater than if saline is given alone[1057]. As with the mercurial diuretics and with water, overdosage with certain xanthines (theophylline, caffeine) decreases their diuretic action, a phenomenon not ordinarily seen with lyuretic diuretics.

Three newer chloruretic diuretics related to the xanthines, and which will be referred to here as *xanthinoids* (containing the group N—C—N several times in the molecule) have been studied by Lipschitz and Stokey[671, 673]. These are melamine, adenine, and formoguanamine. In the normal rat melamine is ecuretic, while adenine and formoguanamine are not. Pitressin does not antagonize these diureses.

The fact that urea, biuret, and the xanthines contain the same N—C—N group at least once in the molecule and are diuretically active, opens the possibility that urea may not be simply a lyuretic diuretic but may exert some specific renal influence. Lipschitz[668], after testing about 50 substances from this viewpoint, arrived at the following conclusions. (*1*) Acid amides are diuretics, but weaker ones than urea. The activity is decreased with the higher molecular weight. (*2*) α-oxy-acid amides are more active diuretics than the corresponding acid amides. (*3*) Urea and simple urea derivatives are about equally active. (*4*) Substances of the aliphatic type containing more than one N—C—N group are more active than urea: biuret, 1.4,* aminobiuret hydrochloride, 9.1. (*5*) The furyl and amidine groups enhance diuretic activity: furoamide, 13, acetamidine hydrochloride, 7. (*6*) Among the cyclic compounds containing the N—C—N group once or several times, there are substances which by far surpass the xanthine diuretics in activity and harmlessness: melamine, 77; adenine sulfate, 139; and formoguanamine, 347. (*7*) It appears that urea and the xanthines are only well known examples of a class of diuretic substances.

* The diuretic activity. See table XXI, § 83.

Miscellaneous Diureses

8.20. *Colloids.* The diuretic behavior of plasma, concentrated albu- min, or acacia[291, 498, 628, 713] is uncertain. Diuretic effects ar obtained at some times and not at others, and no satisfactory rationale accounts for the frequencies with which significant augmentations of urine flow may be observed In edema associated with hypoproteinemia, interstitial fluid is presumably drawn into the plasma as its oncotic pressure is raised following appropriate transfusions of concentrated colloid solutions This constitutes a so-called "mobilization" of edema

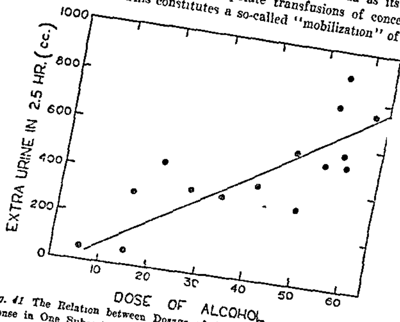


Fig. 41 The Relation between Dosage of Alcohol (Grams) and Diuretic Response in One Subject When the Volume and Other Constituents of the Drink Were Kept Constant. The drink in all experiments was 200 cc in volume (70 per cent cider) and varied only in its alcohol content. After Eggleton [317]

fluid. At the same time, theoretically, there should be some tendency o decrease glomerular filtration by the same principle. Since it is nlikely that an excessive glomerular filtration rate, stemming from educed oncotic pressure, could alone be responsible for the positive ater balance of edema, the mechanism of colloid ecuresis in the intact imal remains in doubt (§5 6, 7.14)

Repeated administration of concentrated serum albumin in nephrotics duces sodium lyuresis but no necessary diuresis[691], but in normals, um antilyuresis may occur[444]. Bryan et al.[194] find that lower-

ing plasma protein by plasmapheresis increases the capacity of the organism to retain normal salt solution Gelatin has been reported to hinder [606, 874] or to favor[1021] diuresis Bridger et al [164] obtained different effects of 6 per cent gelatin in unanesthetized dogs, depending on whether it was unautoclaved or autoclaved The former was found to be an ecuretic diuretic while the autoclaved material was not particularly effective in increasing urine flow

8 21 *Ethyl Alcohol* In normal human subjects, a specific diuretic action of ethyl alcohol is revealed by comparison of its aqueous solutions with plain water (Fig 41) Murray[802] and Eggleton[317, 321] have determined that diuresis caused in part by alcohol is, like water diuresis, inhibited by pituitrin Diuresis seems to be initiated by increase in alcohol concentration in the blood and it fails to be maintained if this concentration is kept steady Urine is consistently more acid during alcohol diuresis[319], a phenomenon not traceable to increased excretion of acetic or acetoacetic acid The behavior of chloride is similar to that in plain water diuresis[325, §8.7]. The mechanism of alcohol diuresis is unknown Although the percentage of alcohol eliminated in the urine varies with the amount ingested, most of it (99 per cent) leaves the body through oxidation [473] The concentration of alcohol in the water of the urine is independent of the urine flow and is the same as in the water of the plasma except when plasma levels are changing rapidly[317] Other ingredients than alcohol and water in beverages do not contribute significantly to the diuresis

It is obvious that much of the diuretic effect following ingestion of alcoholic beverage stems from two sources other than the alcoholic content First, the unavoidably consumed water would of itself bring on diuresis even in the absence of alcohol Second, "social" drinking often involves the intake of water in beverages when there is no negative water load to favor the deflection of some of the ingested water from the kidneys to the tissues

8 22 *Digitalis.* Withering[1167] first described the diuretic property of *Digitalis purpurea.* It has since become commonly accepted that its primary action, and that of derivatives, is less on the kidney than on the heart and circulation[268, 1015] In the absence of heart disease, digitalis has little diuretic effect. Mokotoff et al [779] presented evidence that in heart failure the renal blood flow may be reduced to one-third normal and the glomerular filtration rate to two-thirds normal.

MISCELLANEOUS DIURESES

8 20. *Colloids* The diuretic behavior of plasma, concentrated albumin, or acacia[291, 498, 628, 713] is uncertain Diuretic effects are obtained at some times and not at others, and no satisfactory rationale accounts for the frequencies with which significant augmentations of urine flow may be observed. In edema associated with hypoproteinemia, interstitial fluid is presumably drawn into the plasma as its oncotic pressure is raised following appropriate transfusions of concentrated colloid solutions This constitutes a so-called "mobilization" of edema

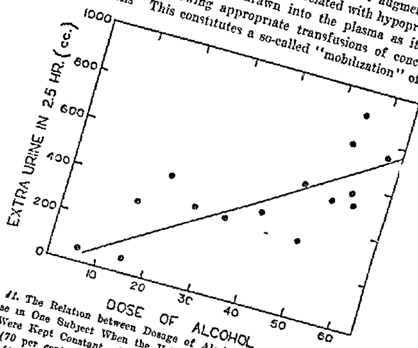


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Repeated administration of concentrated serum albumin in nephrotics produces sodium lyuresis but no necessary diuresis[691], but in normals, sodium antilyuresis may occur[444]. Bryan et al.[194] find that lower-

ing plasma protein by plasmapheresis increases the capacity of the organism to retain normal salt solution. Gelatin has been reported to hinder [606, 874] or to favor [1021] diuresis. Bridger et al.[164] obtained different effects of 6 per cent gelatin in unanesthetized dogs, depending on whether it was unautoclaved or autoclaved. The former was found to be an ecuretic diuretic while the autoclaved material was not particularly effective in increasing urine flow.

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It is obvious that much of the diuretic effect following ingestion of alcoholic beverage stems from two sources other than the alcoholic content. First, the unavoidably consumed water would of itself bring on diuresis even in the absence of alcohol. Second, "social" drinking often involves the intake of water in beverages when there is no negative water load to favor the deflection of some of the ingested water from the kidneys to the tissues.

§ 22. *Digitalis.* Withering[1167] first described the diuretic property of *Digitalis purpurea*. It has since become commonly accepted that its primary action, and that of derivatives, is less on the kidney than on the heart and circulation[268, 1015]. In the absence of heart disease, digitalis has little diuretic effect. Mokotoff et al.[779] presented evidence that in heart failure the renal blood flow may be reduced to one-third normal and the glomerular filtration rate to two-thirds normal.

These considerations suggest a relation between circulatory embarrassment and renal dysfunction yet a few points remain refractory to inclusion in this hypothesis. In the first place the diuresis of digitalis in the presence of edema is an ecuresis, a specific removal of water and salt from the body through the kidneys. But there is actually little impairment of water diuresis[258] or water ecuresis[446] in cardiac failure although definite "impairment" (§7.14) exists in the excretion of salt[392, 1115]. The renal impairment is largely confined to the ability of the kidney to remove loads of saline, while the faculty of regulating plasma concentrations of sodium and chloride is not seriously disturbed. Secondly, in the development of cardiac decompensation, edema may form through emuresis before venous pressure rises[773, 1115] or when these pressures are not elevated[147, 148, 1025]. As Fremont-Smith[380], Warren and Stead[1115], Briggs et al [170], and others[392, 495] have suggested, depression of renal function other *than in consequence of direct renal circulatory embarrassment may have* a role in the retention of edema fluid. The mechanism of such renal impairment is in doubt (§7.14).

Pfaff[845] and Bartram[82] are among the few investigators who have found an increased urine flow in the nonedematous animal following administration of cardiac glucosides *None has demonstrated clear* effects of this drug directly on the kidney[465, 717]. It would be interesting to learn whether digitalis exerts a diuretic or ecuretic effect when it acts directly, and only, on the kidney in cardiac disease.

8 23. *Urine, Renin, etc* Little et al [674, 676] report that intravenous infusion of urine in dogs can promote ecuretic diuresis. If urine is injected too rapidly, collapse and death ensue The substance responsible is thought to have a large molecule.

Extracts of rabbit kidney, containing renin, can produce diuresis and chloruresis when injected into rabbits[163, 851]. Witte's peptone[454] is said to be ecuretic Under certain conditions some anesthetics are diuretic[626], for example, paraldehyde, chloral hydrate, chloralose, and ether[504]. Human hemoglobin injected into rats produces diuresis[666].

A posthemorrhagic diuresis, not related to water drunk is described by Stewart and Rourke[1033] in fasting dogs After hemorrhage there is an immediate potassium lyuresis but no change in the excretion of sodium, chloride (§7 14), or nitrogen. On the second day after hemorrhage the diuresis occurs.

A discussion of the phenomenon of "puncture diuresis" observed by Bernard[105] to follow pricking of the floor of the fourth ventricle (funiculus teres) is given by Cushny[268] The hydruria after an attack of angina pectoris has been considered to involve a nervous mechanism of this type[698].

8 24 *Hormones* Diuretic effects of hormones are discussed in Chapter X. Hormones possessing diuretic action (Table XXV) include those of the thyroid, adrenal medulla, adrenal cortex, anterior pituitary (extract), and the posterior lobe of the pituitary (oxytocic).

8 25 *Hyperventilation* Collip and Backus[235] and Davies, Haldane and Kennaway[284] studied the diuresis observed in most cases where hyperpnea is prolonged for about one hour In this type of diuresis one finds alkalinuria or decreased urinary acidity, lowering of plasma *bicarbonate level, fall in alveolar carbon dioxide, and decreased* excretion of ammonia. If 6 per cent carbon dioxide is breathed for prolonged periods, there is also a diuresis but this is characterized by increased acid and ammonia excretion

McCance and Widdowson[746] showed that hyperventilation diuresis* was accompanied by an increased excretion of sodium and potassium. Briggs[167] pointed out the lack of proportionality between the increase in fixed base excretion and the drop in ammonia production, a fact which he takes to argue against the alleged base-saving properties of ammonia (§7 26) The experiments of McCance and Widdowson were carried out not only in normal subjects but also in salt deficient ones (Tables XXIII, XXIV). In the latter it was found that overbreathing causes no change in urinary pH, no increased excretion of sodium and potassium, an oliguria, and a depression of renal function indicated by aberrant excretion of urea, sulfate, phosphate, and creatinine. These effects are apparently related to the alkalosis of overbreathing rather than to the overbreathing *per se*, since if carbon dioxide is taken during overbreathing, there is no depression of the excretory function Since the lack of alkalinuria in hyperventilation with salt deficiency depends on the lack of sodium in the body, these experiments support the idea that the regulation of plasma osmotic pressure takes some precedence over the regulation of plasma pH It is as if the lack of carbon dioxide

* Also referred to as "bicarbonate diuresis"[10].

in the plasma in hyperventilation lowers the threshold of sodium and bicarbonate, but not below the concentrations which may actually exist in experimental salt deficiency. Excessive plasma carbon dioxide appears to elevate the bicarbonate threshold. In either case, gaseous exchange influences renal function[735]

TABLE XXIII

Effect of overbreathing on the urine in normal and salt deficient persons with respect to urinary flow (u), urinary reaction (pH), and rates of excretion (uU) of various solutes[742]

	Normal	Salt Deficient	
	Breathing air	Breathing air	Breathing a CO_2-air mixture
pH	Becomes alkaline	No change	No change
u	Increases considerably	Decreases considerably	No change
uU_{Na}	Increases	Decreases, but traces only are present both before and during overbreathing	No change
uU_{K}	Increases	Slight decrease, normal amounts present	
uU_{Cl}	Increases slightly	Decreases, but traces only are present both before and during overbreathing	
uU_{urea}	No change	Decreases considerably	Very slight decrease
$uU_{creatinine}$	No change	Decreases considerably	No change
uU_{SO_4}	No change	Decreases considerably	No change
uU_{PO_4}	No change*	Decreases considerably	No change

* Brown et al [177] find a decreased excretion of phosphate in men hyperventilated by means of a respirator with an over-all retention of phosphate during prolonged hyperventilation (8 and 24 hours). Nevertheless plasma inorganic phosphate, as well as plasma sodium and bicarbonate concentrations, fell.

8.26. *Anoxia, Barometric Pressure, and Partial Pressure of Oxyge*

Anoxia has both diuretic and antidiuretic effects[1036, 1068, 1083]. I dogs under anesthesia, respiration of gas mixtures low in oxygen pro duces either polyuria or oliguria, the former generally under mild anoxia and the latter under severe oxygen deprivation. The incidence of either is affected by the type of anesthetic used. The incidence of increased urine flow passes through a maximum when the gas mixtures contain about 11 per cent oxygen. In rats exposed to low barometric pressures (15,000 feet; 440 mm mercury) a polyuria tends to set in according to Silvette[979, 981] although this is partially masked by increasing

TABLE XXIV

Changes in the blood of one subject during salt deficiency[742].

	Normal	Salt Deficient
Cell count (mil./cu. mm.)	4.96	5.95
Hemoglobin (per cent)	101	126.
Cell volume (per cent)	45.6	50.3
Protein, serum (per cent)	6.1	7.3
Urea (mg. per cent)	30	81.
Chloride, plasma (mEq./l.)	100	80.
Chloride, corpuscles (mEq./l.)	52.7	39.5
Sodium, serum (mEq./l.)	151	139.
Potassium, serum (mEq./l.)	4.1	4.2
Alkaline reserve (vol. per cent)	61.4	63.3

respiratory loss of water from the accompanying hyperpnea of anoxic anoxia[1043]. That the effect on the insensible water loss is due to anoxia is shown by its occurring in atmospheres low in oxygen at normal pressure, and not in low pressure atmospheres of sufficiently high oxygen content. Of the four types of anoxia in Barcroft's classification, anoxic anoxia is the only one which leads to polyuria in rats[981]. This can be inhibited by postpituitary extract[980]. Kidneys of rats which have been returned to room pressure for a month following exposure to low barometric pressure show extensive parenchymatous damage, calcification, shrinkage of the stroma, and ischemia[601].

Armstrong[48] has shown that human subjects exposed for several hours to atmospheres at 12,000 feet (490 mm mercury) develop diuresis and decreased urinary specific gravity. The specific gravity does not vary inversely (strictly) as the urine flow because of lyuresis which is greater at greater flows. In human subjects exposed to 18,000 feet (385 mm mercury) or subjected to similar anoxic anoxia by inhalation

of 14 per cent oxygen[101], there is diuresis and lyuresis of sodium, potassium, and chloride[202]. Dogs exposed to high altitudes also show lyuresis of these ions. Following adrenalectomy this lyuresis of sodium and potassium is not present (§10 15).

Silvette and Britton[985] have described in rats an acceleratory oliguresis and a postacceleratory diuresis ("acceleratory polyuria") which were thought referable to anoxia brought about by renocirculatory disturbances During exposure to positive or negative gravitational stress urinary secretion was suppressed. Following centrifugation the urinary flow increased to 40 per cent above normal for 5 to 6 hours The diuresis was *reversed or inhibited by posterior pituitary extract*. Repeated daily exposure for 3 weeks caused albumin to appear in the urine and pathological changes were observed in the kidney.

Ordinarily there is no simple relation between renal oxygen consumption and the excretion of water either in intact animals[77, 162, 608, 1088] or in the isolated kidney[624]. Presumably oxygen consumption is more closely related to nonexcretory renal processes, the efficiency of the kidney being so low in terms of osmotic work (§4 2). In man the resting oxygen consumption of the kidney is approximately 10 3 cc / min.[162]. The oxygen pressure in the urine probably reflects an equilibrium with kidney tissue[707, 709]. This is less likely for carbon dioxide pressure[920]. In normal human urine oxygen tensions lie between 23 and 101 mm of mercury (average, 76 mm in healthy adults). The tension is elevated in high diuresis (95 mm) and lowered in cardiac disease (48 mm.). Carbon dioxide tension in human urine varies from 43 to 102 mm. of mercury with an average of 81 mm It is probably never less than the carbon dioxide tension of arterial blood. In the dog the partial pressure of carbon dioxide of acid urine has been found similar to that of arterial plasma[865] In alkaline urine it is greater A urinary carbon dioxide tension of 310 mm has been reported[65]

Linzbach[665] has suggested that an important fraction of the oxygen used by the tubular epithelium is obtained from that dissolved in the glomerular filtrate, that is, there is a significant urinary as well as vascular source. This supposedly would be available only when the nephron was functioning and that proximal region where most fluid may be reabsorbed would thus be served. Failure of this urinary oxygen supply is thought to account for certain pathological phenomena in nephritis and nephrosis Earlier, Richards and Schmidt[901] had suggested that in frogs, blood flow through the glomerulus was a *function of the call for oxygen* but this was not supported by the work of Adolph[13] for this species (§3.14). And Oliver[828] has shown that a tubule can exist without an intact and functioning glomerulus.

Aglomerular nephrons have a blood supply that is adequate for maintenance and growth in spite of the obliteration of the capillary bed of the glomerular tuft. This is a compensatory blood supply through the vessel of Ludwig which shunts the blood from the afferent arteriole directly into the intertubular capillary system In the progress of disease afferent vessels decrease in size while Ludwig's vessels become more prominent.

Barach and Richards[61] have observed an ecuretic effect of atmospheres high in oxygen, in cardiac edema (§7 14).

§ 27. *Hypnosis Conditioned Reflexes* A number of curious "psychic" diureses have been reported Heilig and Hoff[510] state that under hypnosis the suggestion of pleasure and joy is oliguretic and antilyuretic while the suggestion of unhappiness and misery leads to ecuresis (relative to the unhypnotized person or to joy-suggested ones) with salt loss. Marx[729] hypnotized patients and suggested, when an empty glass was brought to their lips, that they had taken water. A typical "water" diuresis followed which depended on the suggestion of drinking water and not the hypnosis per se. After the experiment his subjects showed spontaneous thirst as if a result of the water they did not take but which brought about ecuresis!

Diuresis can be occasioned through conditioned reflexes[454, 469]. Bykow and Berkmann[206, 207, 208] established a conditioned reflex in the dog by repeatedly putting water into the rectum on different occasions After the reflex had been established the water might be placed in the rectum and then removed and diuresis would still result The animal could be conditioned to the insertion of the rectal tube alone, or to the sound of a whistle even when no water was actually placed in the rectum Finally, placing the dog in the room where the injection was customarily made provoked diuresis The conditioned reflex and its extinction occur in dogs with one kidney denervated This suggests that the reflex has two parts, nervous and humoral, since the effector side of the reflex is not simply nervous. Marx[731] was able to establish a conditioned reflex for diuresis in only one out of four dogs where the conditioned stimulus was a musical signal and the unconditioned stimulus was a pan of milk-water mixture Five months of training were required

§ 28. *Body Position Abdominal Pressures.* Linossier and Lemoine[663, 664] discovered that the erect posture decreases notably

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828. *Body Position. Abdominal Pressures.* Linossier and Lemoine[663, 664] discovered that the erect posture decreases notably

of 14 per cent oxygen[101], there is diuresis and lyuresis of sodium, potassium, and chloride[202]. Dogs exposed to high altitudes also show lyuresis of these ions. Following adrenalectomy this lyuresis of sodium and potassium is not present (§10.15).

Silvette and Britton[985] have described in rats an acceleratory oliguresis and a postacceleratory diuresis ("acceleratory polyuria") which were thought referable to anoxia brought about by renocirculatory disturbances. During exposure to positive or negative gravitational stress urinary secretion was suppressed. Following centrifugation the urinary flow increased to 40 per cent above normal for 5 to 6 hours The diuresis was reversed or inhibited by posterior pituitary extract. Repeated daily exposure for 3 weeks caused albumin to appear in the urine and pathological changes were observed in the kidney.

Ordinarily there is no simple relation between renal oxygen consumption and the excretion of water either in intact animals[77, 162, 608, 1088] or in the isolated kidney[624]. Presumably oxygen consumption is more closely related to nonexcretory renal processes, the efficiency of the kidney being so low in terms of osmotic work (§4 2). In man the resting oxygen consumption of the kidney is approximately 10 3 cc/min.[162]. The oxygen pressure in the urine probably reflects an equilibrium with kidney tissue[707, 709] This is less likely for carbon dioxide pressure[920] In normal human urine oxygen tensions lie between 23 and 101 mm of mercury (average, 76 mm in healthy adults) The tension is elevated in high diuresis (95 mm.) and lowered in cardiac disease (48 mm.). Carbon dioxide tension in human urine varies from 43 to 102 mm. of mercury with an average of 81 mm It is probably never less than the carbon dioxide tension of arterial blood. In the dog the partial pressure of carbon dioxide of acid urine has been found similar to that of arterial plasma[865]. In alkaline urine it is greater. A urinary carbon dioxide tension of 310 mm has been reported[65].

Linzbach[665] has suggested that an important fraction of the oxygen used by the tubular epithelium is obtained from that dissolved in the [illegible] filtrate, that is, there is a significant urinary as well as vascular source. This supposedly would be available only when the nephron was functioning and that proximal region where most fluid may be reabsorbed would thus be served. Failure of this urinary oxygen supply is thought to account for certain pathological phenomena in nephritis and nephrosis Earlier, Richards and Schmidt[901] had suggested that in frogs, blood flow through the glomerulus was a function of the call for oxygen but this was not supported by the work of Adolph[13] for this species (§3 14). And Oliver[828] has shown that a tubule can exist without an intact and functioning glomerulus

Aglomerular nephrons have a blood supply that is adequate for maintenance and growth in spite of the obliteration of the capillary bed of the glomerular tuft. This is a compensatory blood supply through the vessel of Ludwig which shunts the blood from the afferent arteriole directly into the intertubular capillary system. In the progress of disease afferent vessels decrease in size while Ludwig's vessels become more prominent.

Barach and Richards[61] have observed a diuretic effect of atmospheres high in oxygen, in cardiac edema. [714]

§27. *Hypnosis. Conditioned Reflexes.* A number of curious hypnotic diureses have been reported. Heilig and Hoff[510] state that under hypnosis the suggestion of pleasure and joy is oliguretic and antidiuretic while the suggestion of unhappiness and misery leads to diuresis (relative to the unhypnotized person or to joy suggested ones) with salt loss. Marx[730] hypnotized patients and suggested, when an empty glass was brought to their lips that they had taken water. A typical "water" diuresis followed which depended on the suggestion of drinking water and not the hypnosis per se. After the experiment his subjects showed spontaneous thirst as if a result of the water they did not take but which brought about diuresis.

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§28. *Body Position. Abdominal Pressures.* Linossier and Lemoine[663, 664] discovered that the erect posture decreases notably

increased filtration through the remaining glomeruli. It is conjectural how the remaining part of an excised kidney is apprised of the reduction of renal tissue (§4.17, §5.3). Verney suggested that this type of polyuria is found in certain chronic nephritides, constituting a "compensation"[1095]. Removal of an entire kidney results in an increased blood flow, oxygen consumption, and urea clearance in the remaining kidney[1088], the maximum increases being reached in about a month in the dog. The reaction of the reduced kidney to sodium sulfate and to pituitrin is diminished[505].

§32. *Diuresis and Renal Function in Relation to Age.* Renal function differs with age, being poor by adult standards in very young animals and showing some decline in age (§4.8, 4.11). The subject of renal function in early life has been reviewed by McCance[745].

In the newborn infant an average daily urine output (approximately proportional to fluid intake) is given as follows[925]: first day, 15.6 cc.; second, 27.7, third, 54, fourth, 105, fifth, 148, and sixth, 195.5. Despite the small volumes the specific gravity is no higher than 1.012 on the first day and it may fall to 1.003 or 1.004 by the sixth. Thomson[1059a] presents a detailed study of urine formation (reflecting the onset of lactation and establishment of breast feeding) in newborn breast fed infants during the first few days of life, including average figures and ranges for urinary volume, specific gravity, pH, chloride output, etc. In general his results indicate that in this early period volume and urea output increase gradually, pH moves toward alkalinity. Specific gravity rises to a maximum of 1.025 on the third day and then steadily declines till the eighth day following which it becomes more stabilized. Albumin is quite consistently present at the second to fifth days after birth and even more frequently in premature infants.

Barnett[79], using a value equivalent to the velocity constant of inulin (slope of the curve of log blood inulin concentration against time, when inulin concentrations are falling after a priming dose), demonstrated the proportionality of this factor to the inulin clearance (§3.23). Human infants 4 to 9 days old have velocity constants of inulin only one third those of the normal adult. In parallel, infants 7 to 14 days old have reduced urea and mineral clearances and show somewhat elevated serum levels of chloride, sodium, and potassium. They do not have a concentration ratio for chloride over 1 and are unable to form a hypertonic urine[751].* As a result, oliguria becomes synonymous

* In the first two days of extrauterine life infants excrete a comparatively concentrated urine (400 milliosmolar).

With continued exposure to cold, diuresis reaches a maximal flow in the second hour and rapidly diminishes thereafter. Silvette[981] reports polyuria in rats which increased with lower temperatures and decreased with raised temperatures in the range 10° to 30° C This may be related to higher food intakes in the cold.

Cold has the effect of causing temporary albuminuria[571], diminution of blood and plasma volume[22, 91], and increase of plasma concentration as measured by refractive index, hematocrit, and vapor pressure[64]. Some of the fluid lost from the plasma is thought of as appearing in the urine of cold diuresis, possibly as an indirect effect of intense vasoconstriction which reduces the space within which the blood is contained. It is interesting to observe, however, that the fluid shift in cold diuresis is opposite to that in recumbence diuresis (§8 28)

Cooling the blood perfusing the isolated kidney from body temperature to anywhere in the range 3° to 13° C. changes the composition of the urine substantially to that of a serum transudate. There is recovery on rewarming With cooling, urine flow increases reaching a maximum at about 10° C. The chloride concentration of the urine, always low at body temperatures, is increased by cooling so that below about 18° it is the same as the serum concentration[114]. The application of heat to the kidneys appears to have less marked effects[129]. Body temperature has been reported to affect the maximal urinary concentrations of urea and chloride[237].

8.31. *Decreased Renal Mass.* According to Tuffier[1074] and Bradford[159, 160] about 1 to 2 grams of secreting kidney parenchyma per kg body weight are required for life in the dog (equivalent in man to 80 to 100 grams or about one-quarter to one-third of the total renal mass). When a portion of one kidney is excised, there is an increased urine flow (§8 5), sometimes transitory, and not accompanied by appreciable lyuresis. Excision of portions of both kidneys is followed by a more considerable and more permanent hydruria Removal of about two-thirds of the total kidney mass leads to a large and practically permanent polyuria, still with little lyuresis * Loss of three-quarters of the total kidney mass induces polyuria including urea lyuresis

Verney[1094] duplicates the polyuria in the remaining part of an excised kidney by tying arterial branches in the isolated kidney, obtaining an immediate response. Hayman et al.[505] believe there is an

* In an older usage, "polyuria" implied lyuresis along with increased urinary flow, the latter alone, being known as "hydruria"

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with renal insufficiency, and normal saline is a dangerous drug since the kidney cannot regulate loads of water and salt from such solutions in the usual way (by forming a hypertonic urine). Postpituitary extract which produces inhibition of water diuresis in adults has only a very slight and fleeting effect on the urinary concentration of newborn infants producing hypotonic urine, according to Heller[518, 519]. The posterior pituitary glands of the newborn have considerably less of *the antidiuretic and oxytocic principles than do adult glands, but not* so little as to account for the low concentration of infant urine[525] Presumably the sensitivity of the tubules to these hormones is less in the infant than in the adult Heller[518] regards the daily fluid intake as a more important influence on the urinary concentration Barnett et al [80] find that the premature infant does respond to the antidiuretic hormone by an increased tubular reabsorption of water but water deprivation is more effective than the hormone in raising the concentration ratio of inulin

The postnatal development of water diuresis has been studied in pups by Adolph[15, 16]. Within a few days of birth, water to the extent of 5 per cent of the body weight given to dogs by stomach tube makes no difference in the urine flow or weight loss. Sometime around the fifth to twenty-first day water diuresis is acquired and the adult response is fully developed The deficiency in water diuresis before this time is not due to lack of absorption from the gut, a finding which has been affirmed by Heller[520] for the newborn rat

The differences between infant and adult kidneys can be summarized[286, 744] as follows in the infant excretion of water is defective by adult standards, the osmotic pressure of the urine is low and only rises to adult levels when serum values are highly abnormal; glomerular filtration is low and varies with the hydration of the body unlike the adult; urea and mineral clearances are low and the latter may account for the high susceptibility to edema when normal saline is given

As in full term infants, the renal function of premature infants is reduced but to a greater degree They have lower urea, sodium, and chloride clearances than full term infants[*445, 1185*] and the concentration ratio for osmotic pressure (approximated by adding the concentration of electrolytes and urea in the urine and dividing this by the sum of the concentration of electrolytes and urea in the plasma) is usually below 0 5 although it can rise above 1 if the blood urea is high. The functional differences between adults and full term infants are exaggerated in premature infants Wells et al [274, 1120] have shown that injection of concentrated urea solutions (50 per cent) under the skin of fetal rats accelerates urine formation, and thus that some

uretic function at this early age exists However, McCance and Wilkinson[750] were unable to obtain diuresis in suckling rats (unlike adults) by oral 10 per cent sodium chloride, but there was some lyuresis. An old observation of Dastre and Loye[283] suggests that it is not always possible to reach isorrhea in young dogs when 0 7 per cent saline is injected intravenously, unlike the case with adult dogs.

There are significant differences in renal function in old animals as compared with younger adults or very young animals Some of these have been noted previously (§4 8) MacNider[701] states that old dogs anesthetized with ether tend to become anuric, unlike young ones, but that they react much as younger animals to diuretics.

EXTRARENAL VERSUS RENAL ACTION OF DIURETICS

8 33. *The Proximate Action of Diuretics* In the older literature more attention was paid to the idea that diuretics exerted their action on the tissues or the blood rather than on the kidney Thus, Jendrássik[570] believed the diuretic action of calomel resulted from dilution of the blood through the absorption of fluid from body cavities. However, von Schroeder[947, 948] considered xanthines to act directly on the kidneys since no primary change in tissue fluids was observed following their administration Diuretics were supposed to have a primary extrarenal action by Nonnenbruch[816], Bohn[144, 145, 146], Crawford and McIntosh[256], Bieter and Wright[119], Melville and Stehle[766, 767] Claussen[226], Tezner[1052], Stewart[1032], Fischer[365], Curtis[262], Eppinger[345], and others The evidence for this view is of several types

First, there is the finding of hydremia and hypochloremia in normal or nephrectomized dogs following administration of mercurial diuretics or certain xanthines An action by mercury upon body and blood proteins, as indicated by progressive changes in the ultramicroscopic picture of blood plasma particles, has been thought to signify their progressive dehydration and liberation of chloride, making water and chloride more available for renal excretion. Another aspect of this hydremic action is seen in the decreased plasma specific gravity and the increased blood volume which have been said to precede the onset of diuresis[1032]. And the prolonged diureses which can be seen in edema conceivably argue for an extrarenal mobilization of fluid otherwise in poor renal contact (§5 4). For the most part this mobilization concept depends on the subsidiary hypothesis that blood dilution is a stimulus for diuresis, which in itself cannot be accepted without damaging reservations (§8 35).

A second type of evidence for extrarenal diuretic action (on the tissues) is that of Tezner[1052] who found that in children subcutaneous potassium iodide is more rapidly absorbed following novasurol (merbaphen) injection and takes longer to appear in the saliva. Edlund and Linderholm[316] found increased absorption of colloid (hemoglobin), and particularly of water, from the knee joints of rabbits treated with mersalyl (salyrgan) during the first hour after the drug was given and before appreciable diuresis had set in. These experiments are of a type which has not yet been sufficiently investigated but it is not clear what significance these reported effects have for diuresis. McClure and Aldrich[28, 754] introduced a test for the presence of edema and pre-edema states, based upon the time required for the disappearance of 0.2 cc of 0 8 per cent sodium chloride placed intradermally. In cases of developing edema the disappearance time of the bleb is shorter than normal. It was supposed that this test reflected variations in tissue affinity for water and salt. However, Govaerts and Bernard[453] showed that paraffin oil, as well as saline, is more rapidly absorbed from intradermal blebs in edema The simple interpretation was then advanced that under the mechanical influence of the edema, channels opened up, facilitating the removal of any introduced fluid mass.

A third type of evidence is similarly indirect and suppositious It lies in that certain diuretic agents such as digitalis which improve the circulation, appear thereby to aid renal function This factor, and "mobilization" of tissue fluid, may actually play a role in bringing on diuresis but there is no clear proof that such is the case (§8 22).

Evidence for a direct renal action of diuretics is given by Govaerts[451, 452], Schmitz[942], Bartram[82], and Bryan, Evans, Fulton, and Stead[194] It takes the following forms

First, there is the direct denial of the hydremic blood changes reported by other authors[194].

Second, there is the finding that while saline appears mainly to increase glomerular filtration in the course of its diuretic action, mersalyl appears to decrease tubular reabsorption of water. The different type of response to saline and mercury has suggested that the action of mercury is not secondary to an extrarenal mobilization of salt[942]. However, the xanthine, euphyllin, increases glomerular filtration and it could be argued, if weakly, that this is evidence of extrarenal mobilization of salt and water. A similarly unsatisfactory situation exists in regard to certain xanthines in the experiments of Bartram[82]. In anesthetized dogs rendered hydremic by intravenous saline, mercurial

diuretics and theocin-sodium acetate when injected in small doses directly into the renal artery of one side produced diuresis on that side but had little effect on the other. Other diuretics such as caffeine citrate, theobromine-sodium salicylate, theophylline-ethylenediamine, urea, and digitan, in contrast, produced approximately the same urinary excretion from each kidney even though only one renal artery had been injected. It was taken that the mercurial diuretics evinced direct action on the kidneys The others were considered to possess, possibly, some extrarenal action Gremels[465] states that mercurials, xanthines, and cardiac glucosides all have a direct effect on the isolated dog kidney.

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A middle ground in the polemic of extrarenal versus renal action is held by Moller[788] and Engel and Epstein[344] The former contends the evidence supports both renal and extrarenal action The direct renal action of mercurial diuretics is seen in the elevation of the concentration ratio for chloride, while the extrarenal action is seen in the hydremia indicated by the dilution of hemoglobin in the blood. The latter authors support the view that hydremia precedes mercurial diuresis and that there is a quicker absorption of a McClure-Aldrich bleb even before diuresis starts They believe that mercury affects the osmotic pressure in tissues and consequently that the changes effected by mercury with respect to tissues in general may logically include parallel changes in the renal tissue itself In this way there is an indissoluble nexus between renal and extrarenal actions

It is presently difficult to decide whether, or how much of, the action of digitalis, of saline solutions, or of mercurial diuretics is at renal or extrarenal loci. Experiments with isolated or other specialized kidney preparations do not settle the question By this means alone there can be no full comparison of the diuresis from solely renal exposure to a diuretic agent, with the diuresis from the agent permitted general access to normal or pathological body tissues. In the past the matter has been adjudicated according to the temper of the investigator and the physiological mores of the time rather than by logical inference from all pertinent facts

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Theory of Diuresis

8 34 *The Diuresis Problem* The physiologist given to the analys of renal function purely in terms of its glomerular and tubular fractior sees diuresis and antidiuresis, as has been said, merely as the ebb an flow in tubular reabsorption or glomerular filtration, and these ar conveniently explained by the intervention of mechanical, circulatory endocrine, osmotic, or toxic influences. Solute excretion or retentio is seen by this physiologist as a matter of tubular capacity for transpor or work, and the excretion of each solute is without too much difficult compartmentalized in a little excretory system of its own[1124].

To another physiologist, concerned *less with nephrodynamics an* more with the urinary function of the kidney as it is evidenced by th sum of complex responses which serve to maintain homeostasis, diuresi *is something else. Urine flow is less capricious a renal variable when viewed as an integral part of the excretion of many materials* The excretion or retention of water has relation to the excretion or retention of other urinary materials, and the organism is seen constantly to be in multifarious states of imbalance or balance, perhaps tending always toward the zero balance Perpetually prodded by loads and deficits, by states of surfeit and paucity, the kidney is seen to defer, to favor, to restrict, or to compromise the urinary excretion of different substances It sacrifices volume to concentration or pH to osmotic pressure, in what may be the best of all possible choices, that is, those consistent with its physiological capacity, which are in the highest interests of the organism

8.35. *The Hydremia Hypothesis of Diuresis.* It was once considered axiomatic that diuresis resulted from an increase of water in the blood Whatever the source of this water, whether exogenous or endogenous (*"from the tissues"*), *it was an easy surmise that an excess would be* eliminated readily through the kidneys Jendrássik[570], Magnus[702, 704], Starling[1024], Cushny[265], Bayliss and Fee[88], Haldane and Priestly*[476, 872, 873], Rioch[907, 908], and others[255, 340]* supported this hypothesis which has essentially three forms.

First, according to Haldane and Priestley the kidneys cannot withhold water from renal excretion when *the diffusion pressure of* water in the urine is considerably below that in the blood In this view (essentially an oversimplified fugacity hypothesis) water diuresis becomes a response to some slight dilution of the blood *which causes an* increase in the diffusion pressure of its water. Second, Rioch believed

that the dilution of the electrolyte concentration of the blood was probably the factor responsible for instigating water diuresis Though inextricably tangled with the diffusion pressure concept, the electrolyte dilution hypothesis emphasizes a different proximate cause of diuresis Third, the dilution of plasma colloids shown by Starling to favor increased filtration of fluid across capillary walls, including those of the glomeruli, is consistent with diuresis ("dilution diuresis").

Attractive as the protean hydremia hypothesis superficially appears, it has possibly fatal defects Experiment reveals situations in which there is no parallelism between water excretion and blood dilution[10, 1058]. In water diuresis the greatest blood dilution precedes the greatest diuresis with a lag of 15 minutes Baird and Haldane[58] drank hypertonic salt solutions followed by varying quantities of water. Extra water consumption was found to have little effect on the course of the moderate diuresis produced by the hypertonic solutions so that the diuresis was in effect independent of the blood dilution. Similarly, Underhill and Pack[1076] found no correlation between hydremia and the diureses of water, intravenous sodium acetate, or intravenous urea solutions Pituitrin administration can produce an enuretic blood dilution, evidencing in this instance a negative correlation of hydremia with diuresis Lack of correlation between hydremia and diuresis is shown by the work of Smirk[992] and Baldes and Smirk[59] who measured blood dilution in several ways (per cent solid in whole blood, hemoglobin of whole blood, hematocrit, protein content of plasma, and chloride content of plasma) In man a fall in the total osmotic pressure of the blood, if produced gradually by mineral starvation, does not lead to the hypothetically expected diuresis If the total osmotic pressure of the blood is first raised artificially and followed by a given dose of water, diuresis may then ensue even if the total osmotic pressure does not fall below normal Baldes and Smirk thought that water diuresis was best interpreted by the hypothesis that a mechanism which resides in the kidney is stimulated directly as a result of a sudden increase in the proportion of water in the blood whereupon there is then a delay before the kidney responds by diuresis to this stimulus Lyuretic diureses from strong solutions such as of salt or glucose argue against the alleged requirement of a hydremia measured in terms of total osmotic pressure of the serum, since this may increase in these diureses.

From studies of the diuretic effect of hypertonic salt solutions taken orally, Arden[46] concluded that blood dilution was not a factor of importance to diuresis because increased urine flow is proportional to the quantity of salt taken, under conditions where water leaves the

Theory of Diuresis

8.34. *The Diuresis Problem.* The physiologist given to the analysis of renal function purely in terms of its glomerular and tubular fractions sees diuresis and antidiuresis, as has been said, merely as the ebb and flow in *tubular reabsorption or glomerular filtration*, and these are conveniently explained by the intervention of mechanical, circulatory, endocrine, osmotic, or toxic influences. Solute excretion or retention is seen by this physiologist as a matter of tubular capacity for transport or work, and the excretion of each solute is without too much difficulty compartmentalized *in a little excretory system of its own*[1124].

To another physiologist, concerned less with nephrodynamics and more with the urinary function of the kidney as it is evidenced by the sum of complex responses which serve to maintain homeostasis, diuresis is something else Urine flow is less capricious a renal variable when viewed as an integral part of the excretion of many materials. The excretion or retention of water has relation to the excretion or retention of other urinary materials, and the organism is seen constantly to be in multifarious states of imbalance or balance, perhaps tending always toward the zero balance Perpetually prodded by loads and deficits, by states of surfeit and paucity, the kidney is seen to defer, to favor, to restrict, or to compromise the urinary excretion of different substances. *It sacrifices volume to concentration or pH to osmotic pressure,* in what may be the best of all possible choices, that is, those consistent with its physiological capacity, which are in the highest interests of the organism.

8.35 *The Hydremia Hypothesis of Diuresis.* It was once considered axiomatic that diuresis resulted from an increase of water in the blood Whatever the source of this water, whether exogenous or endogenous ("from the tissues"), it was an easy surmise that an excess would be eliminated readily through the kidneys. Jendrássik[570], Magnus[702, 704], Starling[1024], Cushny[265], Bayliss and Fee[88], Haldane and Priestly[476, 872, 873], Rioch[907, 908], and others[255, 340] supported this hypothesis which has essentially three forms

First, according to Haldane and Priestley the kidneys cannot withhold water from renal excretion when the diffusion pressure of water in the urine is considerably below that in the blood In this view (essentially an oversimplified fugacity hypothesis) water diuresis becomes a response to some slight dilution of the blood which causes an increase in the diffusion pressure of its water. Second, Rioch believed

that the dilution of the electrolyte concentration of the blood was probably the factor responsible for instigating water diuresis. Though inextricably tangled with the diffusion pressure concept, the electrolyte dilution hypothesis emphasizes a different proximate cause of diuresis. Third, the dilution of plasma colloids shown by Starling to favor increased filtration of fluid across capillary walls, including those of the glomeruli, is consistent with diuresis ("dilution diuresis").

Attractive as the protean hydremia hypothesis superficially appears, it has possibly fatal defects. Experiment reveals situations in which there is no parallelism between water excretion and blood dilution[10, 1058]. In water diuresis the greatest blood dilution precedes the greatest diuresis with a lag of 15 minutes. Baird and Haldane[58] drank hypertonic salt solutions followed by varying quantities of water. Extra water consumption was found to have little effect on the course of the moderate diuresis produced by the hypertonic solutions so that the diuresis was in effect independent of the blood dilution. Similarly, Underhill and Pack[1076] found no correlation between hydremia and the diureses of water, intravenous sodium acetate, or intravenous urea solutions. Pituitrin administration can produce an emuretic blood dilution, evidencing in this instance a negative correlation of hydremia with diuresis. Lack of correlation between hydremia and diuresis is shown by the work of Smirk[992] and Baldes and Smirk[59] who measured blood dilution in several ways (per cent solid in whole blood, hemoglobin of whole blood, hematocrit, protein content of plasma, and chloride content of plasma). In man a fall in the total osmotic pressure of the blood, if produced gradually by mineral starvation, does not lead to the hypothetically expected diuresis. If the total osmotic pressure of the blood is first raised artificially and followed by a given dose of water, diuresis may then ensue even if the total osmotic pressure does not fall below normal. Baldes and Smirk thought that water diuresis was best interpreted by the hypothesis that a mechanism which resides in the kidney is stimulated directly as a result of a sudden increase in the proportion of water in the blood whereupon there is then a delay before the kidney responds by diuresis to this stimulus. Hyuretic diureses from strong solutions such as of salt or glucose argue against the alleged requirement of a hydremia measured in terms of total osmotic pressure of the serum, since this may increase in these diureses.

From studies of the diuretic effect of hypertonic salt solutions taken orally, Arden[46] concluded that blood dilution was not a factor of importance to diuresis because increased urine flow is proportional to the quantity of salt taken, under conditions where water leaves the

bloodstream to enter the gut[240, 1172] in response to the osmotic gradient between the contents of the gut and the blood. An early observation of Frey[384] favored the view that the stimulus in salt diuresis was the absolute quantity of salt taken rather than that of water

Finally, we may note that anesthetics such as amytal and pentobarbital produce hydremia and oliguresis[180, 481]

In general, for any examples one may bring forward of high correlation between hydremia and diuresis, corresponding examples of high negative correlation or zero correlation between these variables can be cited Where it is shown that dilution of plasma colloid promotes diuresis in one case, it may still be shown that in another, low plasma colloid may exist without favoring diuresis We do not know all of the factors which enter these pictures, and unless they are perceived and remarkably clarified, we cannot seriously employ the hydremia hypothesis to account for the fundamental facts of diuresis

8 36. *The Threshold Gap Hypothesis of Diuresis.* An empirical rule formulated by Dillon[298] has been applied to the phenomenon of diuresis, qualitatively accounting for a wide range of experimental results He suggests that the threshold of retention for chloride is held at its normal level by a reflex of an ionic balance between cells and extracellular fluid in the kidney If the plasma concentration of chloride differs from its actual threshold by more than a certain amount (ca. 1 to 2 mEq /l), diuresis results This diuresis will be accompanied by an increase in the urinary concentration of chloride if the threshold has fallen below the actual plasma concentration, and by a decrease if the threshold is raised above the actual plasma concentration

It is unnecessary to detail here objections to this hypothesis which take the form of exceptions to the rule * Principles of renal physiology are not sufficiently developed to permit affirmation or denial, on theoretical grounds, to the threshold gap hypothesis For the present it can only be regarded as an interesting empirical rule of some heuristic value which, to the extent that it holds, will eventually be incorporated into a body of principles of urinary function

* An instance of such an exception is given in the diuresis which results from the infusion of saline solution whose ionic concentrations are at the actual thresholds of chloride and/or sodium, that is, diuresis can obtain with no threshold gap Again, in the lyuretic diuresis following administration of hypertonic sodium chloride the greatest diuresis does not necessarily occur when plasma chloride concentration is maximal[286].

§ 37. *The Postpituitary Hypothesis of Diuresis.* By the hydremia hypothesis an increased concentration of water in the blood is the "immediate" stimulus in water excretion; by the postpituitary (pars nervosa) hypothesis, an increased concentration of water in the blood is the "mediate" stimulus[605]. The postpituitary hypothesis[1026], or as it has been called, the "hypopitressinemia" hypothesis of diuresis is a concept designed to account for the vicissitudes of the urine flow chiefly where these have reference to changes in the water content of the body. It has been forged into a useful tool by Verney and his co-workers[605], by Gilman and Goodman[431], and by Fisher, Ingram, and Ranson[370, §1040].

The postpituitary hypothesis holds that a load of water in the body fluids, through the lowering of osmotic pressure which it produces in these, alters the degree of stimulation of osmoreceptors in the nervous system in the bed of the internal carotid artery. The result of such altered stimulation is a reflex neural inhibition, through the supraoptico-hypophyseal system, of the secretion of the antidiuretic hormone of the pars nervosa. The hormone falls to a level in the blood such that tubular reabsorption of water is decreased and the urine flow is increased. The time required for the hormone to fall below its "antidiuretic threshold" presumably constitutes the latent period of water diuresis. Deficits of water in body fluids, or the introduction of substances which raise the osmotic pressure of the body fluids in the region of the osmoreceptors, have the opposite effect. Release of pituitary antidiuretic hormone is stimulated with a resulting inhibition of urine flow. The postpituitary hypothesis is particularly elegant when applied to the phenomenon of water diuresis and its inhibition through osmotic changes in the body fluids. In its pure form, however, it does not account for diureses in general, and it is necessarily commingled with other hypotheses when applied to diureses referable to certain other agents than water. Thus, while the initial, small diuretic effects of loads of isotonic saline fall in nicely with the lack of osmotic stimulation expected from such solutions, the ultimate polyuria which can follow prolonged, steady state intakes of such solutions is not simply accounted for thereby. The diuretic effects of isotonic sodium sulfate, strong in comparison with those of isotonic sodium chloride[703, 1177], clearly call for qualification of the functioning of the antidiuretic hormone. Further, we may inquire why a water diuresis falls off at all so long as there is an appreciable water load in the body, if the diuresis is due to lack of antidiuretic hormone in the circulation. In a declining water diuresis, the rate of water excretion is related to water load[16]. It has not yet been shown that corresponding gradations in circulating antidiuretic hormone

actually occur in the normal organism, despite the fact that graded antidiuresis may be produced in dogs with diabetes insipidus by regulating the administration of vasopressin[965].

Wesson, Anslow, and Smith[1123, 1124] have applied the postpituitary hypothesis to the excretion of water in the complex state where strong electrolytes such as sodium chloride are being simultaneously excreted (§8.1). They postulate a distal tubular rate of water reabsorption which can be activated to varying degrees by the antidiuretic hormone, that is, between zero per cent (maximum diuresis) and 100 per cent (maximal oliguresis or minimal diuresis) Even with this refinement the matter is left objectionably over-simplified. The evaluation of the influence of other hormones such as adrenal cortical, oxytocic, etc., and of the excretion of other uriniferous solutes has scarcely begun, yet it is almost certain that they must be incorporated into the theory of diuresis Presumably the postpituitary hypothesis will become an important link in this theory connecting presently known and as yet unknown systems of renal regulation.

No one has yet presented a general theory of diuresis. With or without challenge to the fundamental concepts of renal function, that is, that water and other urinary constituents are filtered at the glomerulus and that water, at least, is reabsorbed in variable degree by the tubules, we cannot fully describe the excretion of water and other urinary *materials in a manner which is internally and completely consistent* Neither do we have any compelling reason to think that our explanations for the activity of individual diuretics are sound. It is not enough that it is possible to construct hypotheses which account for large areas of known fact No matter how ingenious these may be, they will have to justify themselves in enabling us to predict previously unknown or unsuspected renal relations, and in indicating how these may be found Schemes which fail to satisfy these tests are wanting in their fabrication

CHAPTER IX

Antidiuresis and Antidiuretics

91 Some of the facts of antidiuresis cannot readily be divorced from those of diuresis or of endocrine control of urinary function, and these are accordingly discussed in other sections of this book. The best known antidiuresis is that which results from the action of the antidiuretic hormone of the posterior pituitary when it stimulates an increased tubular reabsorption of water. Water diuresis is most easily subject to the antagonism of this hormone. Mercurial diuresis is not completely antagonized. Lyuretic diureses such as from sodium chloride, potassium acetate, urea, etc. and some xanthinoid diureses such as of melamine, adenine, and formoguanamine, are relatively uncontrollable. Theophylline diuresis is said to be increased as a result of the action of pituitrin[1078].

Antidiuretics of Neurohypophyseal Origin

92 *Acetylcholine Antidiuresis.* Pickford [852, 853, 855] has studied the inhibitory action of acetylcholine on water diuresis in the unanesthetized dog. After atropine, given to counteract peripheral effects of the parasympathomimetic drug, intravenous acetylcholine led to a temporary inhibition of water diuresis accompanied by a rise in chloride excretion. An initial, brief anuria, not characteristic of pure pituitary antidiuresis but presumably due to some experimentally uncontrolled factor was also observed. Blood pressure changes were not involved in this effect. In a thirsting dog acetylcholine produces a diuresis which is characteristic of postpituitary action in this condition (§102).

Acetylcholine injected into the supraoptic nucleus results in an inhibition of urine flow which is not seen after removal of the pituitary gland[855]. No inhibition follows injection into the mammillary bodies or lateral hypothalamus. Thus acetylcholine appears to act on the central nervous system, possibly by stimulating the supraoptic cells, causing the liberation of the antidiuretic hormone of the pituitary.

93 *Nicotine and Lobeline Antidiuresis.* Burn, Truelove, and Burn[290], interpreting the experiments of Pickford on acetylcholine

as evidencing the "nicotinic" action of this drug, tested the effect of nicotine on water diuresis and concluded that the inhibition which it produces may be due to stimulation of the supraoptic nucleus bringing on a release of antidiuretic hormone from the posterior pituitary. In the rat nicotine is antidiuretic but not if the pituitary has been removed. In man smoking exerts an antidiuretic effect to the extent in a sensitive subject that one cigarette will inhibit diuresis for 2 to 3 hours The same amount of nicotine as contained in this cigarette will give the effect upon intravenous injection. The stimulus of nicotine persists for 30 to 45 minutes even if given intravenously and is thought tonically to discharge pituitary antidiuretic hormone. Some individuals are less sensitive to this effect of nicotine which may in part represent a tolerance to the drug The effect is not due to nausea. Nonsmokers were considered by Walker[1110] to be more susceptible to the antidiuretic influence of smoking than smokers but Eggleton[321] finds that while the reaction of smokers to intravenous nicotine is a diminished diuretic response to water (or ethyl alcohol-water) load, nonsmokers actually show an enhancement of the response. The latter investigator suggests that a possible explanation of this difference lies in a differential action of nicotine on the sympathetic and parasympathetic systems in the two groups. It seems to her not unlikely that subjects addicted to nicotine might respond to a single injection of the drug differently from those whose tissues had not previously been exposed to its action Stimulation of the sympathetic system is known to antagonize the output of antidiuretic hormone (the nonsmoking group) but in smokers it appeared to bring on increased output of hormone (§10 18).

Fugo[389] describes an antidiuresis in normal dogs which follows the administration of the alkaloid yohimbine The polyuria following transection of the posterior lobe is not relieved by yohimbine whose action is attributed to the release of the antidiuretic principle of this

release of some diuretic principle from the anterior lobe

9 4. *Morphine Antidiuresis.* Intramuscular morphine sulfate (10 mg.) can inhibit water diuresis in man producing at the same time slight chloruresis[362]. It does not inhibit saline diuresis to the extent that it does water diuresis. From similar observations in normal dogs and from the fact that morphine does not inhibit water diuresis

in dogs with diabetes insipidus, de Bodo[287] concluded that the neurohypophysis is necessary for the antidiuretic action of morphine. Walker[1110] states that subcutaneous morphine sulfate (20 mg.) in therapeutic doses does not inhibit water diuresis in man.

The renal influence of morphine varies in different animals, for example, it has no clear antidiuretic action in the rabbit in contrast to the dog[514]. The mechanisms of morphine antidiuresis in different species are possibly of three types. Lipschitz and Stokey[672], affirming first the idea of postpituitary mediation of morphine action in the dog show, secondly, that morphine is antidiuretic in the lyuretic diuresis of sodium chloride or the xanthinoid diuresis of melamine and formoguanamine. In other words, it is antidiuretic where acetylcholine, pitressin, or phenobarbital is inactive, or where postpituitary mediation is ineffective.* Since neurohypophysectomized dogs do not show this antidiuretic activity of morphine the mechanism in these instances is suspected to be mediation by the anterior lobe (§9.3) of the hypophysis. This normally stimulates the adrenal cortex which, in turn, is essential for diuresis. Other possibilities include a peripheral action of the drug on the kidney or a depressing effect upon the adrenal cortex. However, White et al.[1134] have shown that demonstrable falls in paraaminohippurate and inulin clearance in dogs, following hypophysectomy, are not due to adrenocortical regression dependent on loss of adrenocorticotrophic hormone. Neither adrenal replacement therapy nor administration of adrenocorticotrophic hormone has any effect in protecting these renal functions. These investigators regard the effects as due to loss of anterior lobe principle (§10.11). Thirdly, in the dog the renal nerves play no part in morphine antidiuresis but in the rat morphine antidiuresis during the action of diuretics, and most of it in water diuresis, is paralyzed when the kidneys are decapsulated and denervated. Only small amounts of the antidiuretic hormone are found in the urine of normal and hydrated rats under morphine.

95. *Thiol (BAL) Antidiuresis.* The action of organic or inorganic mercurial diuretics is prevented or abolished by certain thiols (§817)[482, 1058]. Earle and Berliner[315] find that BAL (British anti-lewisite, 2, 3-dimercaptopropanol) can also inhibit water diuresis, probably by stimulating the secretion of the antidiuretic hormone of the pituitary gland since there is no effect of this drug in dogs with

*It is also antidiuretic and antichloruretic in mercurial diuresis[482] in congestive heart failure (Fig. 42).

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diabetes insipidus In antagonizing mercurial diuresis, BAL exhibits also an antichloruretic effect. Since pitressin of itself will inhibit a mercurial diuresis yet not stop the mercurial chloruresis, these authors *suggest that the mechanism of BAL antichloruresis involves the combining of BAL with mercury.*

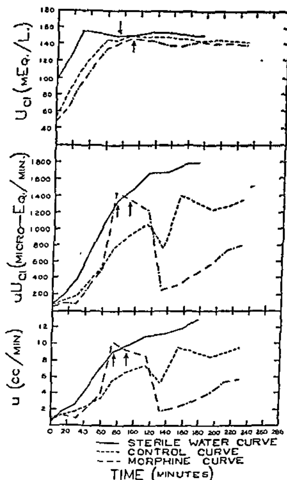


Fig. 43. The Antidiuretic Action of Morphine on Mercurial Diuresis in a *Patient with Congestive Failure* The "*control*" *curve represents* the effect of mercupurin alone The "morphine" curve and the "sterile water" curve represent, respectively, the effect and lack of effect of injections of these on the course of the mercurial diuresis. The arrows to the left in each diagram indicate the time of injection of sterile water; those to the right indicate the time of injection of morphine. Abscissa shows the time in minutes following mercupurin injection After Ferrer and Sokoloff [362].

The chloruretic influence of certain antidiuretics, for example, acetylcholine, supposed to act through pituitary antidiuretic mediation, is difficult to explain if chloruresis is more a property of oxytocic action than of antidiuretic action[377–379, 632]. In this case postpituitary mediation would appear to involve two hormones in these antidiureses, the oxytocic one being intrinsically chloruretic and diuretic but having its diuretic factor masked (§10 3).

9 6 *Postsyncopal Oliguria* Brun, Knudsen, and Raaschou[189, 190, 191] find a fall in water diuresis in the passive erect posture when this is attained after the horizontal position has been held for a time. Brief circulatory collapse brought about in water loaded subjects by means of a tilt table is followed by protracted oliguria which they designate as postsyncopal It is believed that pituitary antidiuretic hormone is brought into action through reflexes involving pressoreceptors * Findings taken to support this view include the facts that changes in chloride excretion during postsyncopal oliguria correspond to changes observed after the injection of antidiuretic hormone, transfusion of blood from recently collapsed subjects into other water loaded subjects is followed by antidiuresis; and patients with diabetes insipidus of moderate severity show a shorter duration of postsyncopal oliguria.

9.7 *Anesthetic Antidiuresis* Ether anesthesia in dogs causes various changes in urine flow including an initial oliguresis followed by some diuresis which may be succeeded in turn by a progressively decreasing output or even anuria[504, 1030]. Ether anesthesia brings on hyperglycemia and reduced plasma volume[94, 739, 996, 1034] and, when deep, a depression of inulin and diodrast clearances[233, 252]. There is a baruria (specific gravity up to 1 057) due in part to 5 or 6 per cent glycosuria † Water diuresis is diminished for a brief period following one hour of surgical anesthesia but the 24 hour urine output is not markedly diminished. Cyclopropane anesthesia depresses glomerular filtration and renal blood flow to a somewhat greater degree than ether[201] It resembles ether and ethylene in depressing urine

* It is interesting to note in this connection that small arterial hemorrhages (6 per cent of blood volume) cause diuretic inhibition of the pituitary type in dogs in which splanchnic nerves have been divided[1098].

† The specific gravity of a 5 per cent aqueous solution of glucose, $D_{4°}^{25°}$, is ca 1 0166 (see table V)

flow. Such depression is, again, followed by compensatory excretion several hours after anesthesia[1116].

Amytal, sodium pentobarbital, sodium pentothal[356, 730, 826, 1113] and other barbiturates[672, 1082] are antidiuretic for water diuresis and to some extent for certain other diureses including those of mercury[978]. These drugs are somewhat oligolyuretic and antilyuretic for substances ordinarily readily eliminated, including phenol red. However, strong, nonwater, diuretic diureses render them antidiuretically inactive[672]. Sodium pentothal followed by pituitrin effects a slight diuresis while pituitrin followed by pentothal results in an oliguresis even more marked than that with pituitrin alone[978].

Intraperitoneal sodium pentobarbital (nembutal) in proper anesthetic doses increases plasma volume[481] in dogs and usually does not impair renal function as measured by diodrast and inulin clearance and *Tm*. When renal failure does occur, it is associated with pronounced oliguresis and with concurrent depression of these clearances, independently of arterial pressure. Blood pressure levels of 110 to 120 mm of mercury which might be normal in conscious dogs may express toxic depression under pentobarbital which otherwise raises blood pressure (§8 6). The onset of severe oliguria, indicating renal failure, is thought to provide a more delicate index of the toxic effects of the anesthetic than a decrease of arterial pressure[242]. Depression of renal function prevents, in part, elimination of toxic doses of anesthetics. Such autogenous inhibition of excretion, however, is characteristic of many substances in overdosage, including water, potassium, mercury, etc. In common with other anesthetics such as urethane and chloroform, barbiturates seem to suppress central impulses by which acetylcholine action or, directly, the secretion of the antidiuretic hormone of the pituitary is inhibited[356]. This view is based on the fact that drugs like phenobarbital, while antidiuretically active in normal dogs, are not active in neurohypophysectomized animals, or in nonwater, diuretic diureses. An unsatisfactory point in this conception is that no antidiuretic principle or hormone is found in the urine of dogs treated with antidiuretic doses of phenobarbital[672, §10 2]. However, it has been supposed that the antidiuretic material is not excreted in appreciable quantities in the urine until relatively high blood hormone levels are reached.

Many other anesthetics including avertin[180], luminal[150, 626], and chloretone[819] have antidiuretic effects whose mechanisms are not always clear. Narcotic action does not necessarily parallel the antidiuretic effect[149, 150]. Chloralose has no such effect even in deep narcosis, and alcohol is actually diuretic in certain doses (§8 21).

Urethane, paraldehyde, and chloral have been reported to be somewhat diuretic[948].

9 8 *Emotional and Psychogenic Antidiuresis* Taking blood from unbound rabbits has no effect on their urine flow[523], but stretching these animals and tying them on their backs brings about a diminution of water diuresis[780] which can be nullified by either narcosis or decortication Water diuresis in normal rabbits even under chloralose-urethane is curtailed by "painful" stimulation in the lumbar region, although similar stimulation in animals with pituitary stalks destroyed causes no antidiuretic response[502] "Emotional oliguria"[174] is correlated with decreased clearances of inulin and paraaminohippurate in the rabbit and is independent of renal innervation

In dogs strong affective stresses such as rage bring on complete anuria which gradually disappears[302] Emotional stress, induced by strange sounds (horn) or subcutaneous electrical stimulation, inhibits water diuresis within 2 minutes[820, 821, 922] Verney[1098] has reviewed the work which demonstrates that the action of emotional stress in inhibiting water diuresis is mediated through the postpituitary, the release of whose antidiuretic principle is facilitated after sympathectomy

Pain in man, induced either by exposure of a limb to an ice-water bath[824] or through the application of a device for exerting pressure on the head[1178], or through circulatory arrest by means of an occlusion cuff on the arm[596], is oliguretic Decreases in diodrast and inulin clearances observed during the period of pain suggest a vasoconstrictive factor in this phenomenon although there is good evidence that reflex stimulation of the neurohypophysis is also involved

Under hypnosis the suggestion of happiness, pleasure, and joy is reported to bring on antidiuresis and water retention[510] It is claimed that in the attempt to produce a conditioned water diuresis reflex (§8 27) there can develop a conditioned inhibition of the unconditioned response, characterized by increase in the latent period of diuresis, decrease in magnitude of diuresis, and finally, by a total lack of diuretic response to water ingestion[314] It is not shown whether or to what extent these phenomena actually derive from postpituitary mediation

9 9. *Increased Osmotic Pressure of Arterial Blood* Verney's[1098] researches have shown how release of postpituitary antidiuretic hormone

Vascular disturbance is not limited to a decrease in the volume of blood reaching the kidney. As has been said there is also observed within the kidney a great alteration in the distribution of blood, entailing a diversion of flow from the cortical glomeruli to and through the juxtamedullary glomeruli (§3 14) Such reduced flow through the cortex has been thought consistent with a reduced glomerular filtration sufficient to induce anuria, as in the "crush syndrome" of Bywaters and Beall[209], while a nutritive flow through the cortex might still be maintained Van Slyke[1086] and others have shown in dogs that total renal blood flow in hemorrhage and traumatic shock is greatly diminished. This condition is distinguished from the instances Trueta mentions in which the diversion of blood flow from the cortex might not result in a reduced *total renal blood flow* Reubi and Schroeder[894] *were unable to obtain* evidence in dog or man that large, intermittent, vascular shunts could be affected by vasoactive drugs such as histamine and epinephrine If such operable shunts exist in these species they have thus far no demonstrable physiological function

9.12. *Antidiuretic "Diuretics"* Diuretic agents, so-called from their characteristic effect on urine flow under given conditions, do not always behave diuretically It has been noted in the previous chapter how overdosage of many diuretics (water, mercury compounds, xanthines, potassium, etc) results in either an inhibition of diuresis, oliguresis, or anuria We suppose the basis of these effects probably to involve toxicity, both renal and extrarenal in varying degrees, rather than a "physiological" antidiuretic action

A lyuretic diuretic such as sodium chloride, administered without water or with small quantities of water, calls forth a characteristic increase in urine flow (Fig 40) Water alone similarly produces its own characteristic increase in urine flow (Fig. 36). Both diuretics are individually ecuretic Yet a water diuresis may be inhibited and made nonecuretic by the administration of sodium chloride[9, 680, 1105], presumably most strongly where the ratio of the loads of salt and water approximate a concentration of saline in the most hydropigenous range (Fig 29) A diuresis from hypertonic sodium chloride is not effectively inhibited when water, *sufficient to make the loaded salt solution isotonic*, is ingested[9]; neither is it increased[46].

Water given intraperitoneally inhibits the specific action of theophylline ethylenediamine (aminophylline)[264], presumably secondarily to the diffusion of salt from the plasma to the peritoneal fluid, which is caused by this procedure. Alkalinizing salts, such as sodium bicarbonate,

which are lyuretic diuretics[10, 46] inhibit the action of mercur
diuretics[344, 348, 349, 924] Calcium chloride orally, otherwise di
retic, has been said to give no diuresis when ingested in isotonic solutio
and to be oligolyuretic for a time[10]. These and other antidiureti
actions of "diuretic" agents are of theoretical and practical interes
but have had little attention thus far from renal physiologists.

9 13 *Ureteral, Intra-abdominal, and Renal Blood Pressures.* Appli-
cation of a resistance to urinary flow through the ureters, raising the
pressure of the urine sufficiently (§8 28), retards the flow[654, 738].
In narcotized dogs the ureteral pressure, which is always less than
arterial, increases with diuresis Urine flow has been obtained at pres-
sures as high as 60 mm of mercury[448, 1054] In the isolated kidney
ureteral pressure of the order of 20 mm almost abolishes urine
flow[1160] Increased pressure is considered to retard filtration at the
glomeruli rather than to disturb renal circulation or to induce a leakage
of fully formed urine from the tubules to the blood[324]

A rise of intra-abdominal pressure in the dog is followed by a progres-
sive diminution of urinary flow in the range from 15 to 30 mm mer-
cury, at the latter point there is suppression of urine formation Venous
pressure below the diaphragm rises with intra-abdominal pressure[1060]
and to almost the same extent (§8 28) In man abdominal compression
by girdle[161, 162], causing a rise in intra-abdominal venous pressure
of 20 mm., results in decreased urine flow, renal plasma flow, filtration
rate, and oxygen consumption Intra-abdominal pressures which pro-
duce oliguresis are higher than those reported to produce diuresis
Since the abdominal musculature loses tonus when fluid is put into the
peritoneal cavity, it is possible for much ascitic fluid to accumulate before
affecting venous pressures Intra-abdominal pressure transmitted to
the venous circulation below the diaphragm may be a factor in deter-
mining the low fugacity of edema fluid in the extremities

Hemorrhagic reduction of systemic blood pressure to 60 to 70 mm
mercury leads to a reduction in urinary flow, but following trans-
fusion restoring normal blood pressure the homaluric rate may be
exceeded[243] In shock urine flow is uniformly reduced and anuria
not uncommon[648] There is concomitant albuminuria, parenchy-
mous renal degeneration, deficient renal function and/or uremia[792]
oliguresis is correlated with depression of inulin clearance and of
circulation[1086].

ppage of the renal arterial blood flow by compression, resulting in
f renal arterial pressure for short periods (1 to 3 minutes) causes

Vascular disturbance is not limited to a decrease in the volume of blood reaching the kidney. As has been said there is also observed within the kidney a great alteration in the distribution of blood, entailing a diversion of flow from the cortical glomeruli to and through the juxtamedullary glomeruli (§3 14). Such reduced flow through the cortex has been thought consistent with a reduced glomerular filtration sufficient to induce anuria, as in the "crush syndrome" of Bywaters and Beall[209], while a nutritive flow through the cortex might still be maintained Van Slyke[1086] and others have shown in dogs that total renal blood flow in hemorrhage and traumatic shock is greatly diminished This condition is distinguished from the instances Trueta mentions in which the diversion of blood flow from the cortex might not result in a reduced total renal blood flow Reubi and Schroeder[894] were unable to obtain evidence in dog or man that large, intermittent, vascular shunts could be affected by vasoactive drugs such as histamine and epinephrine If such operable shunts exist in these species they have thus far no demonstrable physiological function

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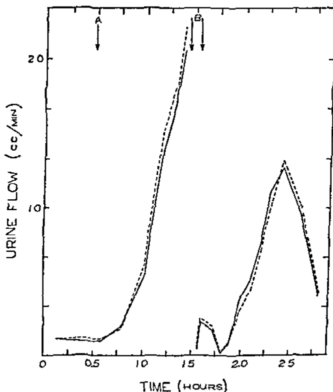
9 13 *Ureteral, Intra-abdominal, and Renal Blood Pressures.* Appl cation of a resistance to urinary flow through the ureters, raising the pressure of the urine sufficiently (§8 28), retards the flow[654, 738]. In narcotized dogs the ureteral pressure, which is always less than arterial, increases with diuresis Urine flow has been obtained at pressures as high as 60 mm. of mercury[448, 1054] In the isolated kidney ureteral pressure of the order of 20 mm almost abolishes urine flow[1160] Increased pressure is considered to retard filtration at the glomeruli rather than to disturb renal circulation or to induce a leakage of fully formed urine from the tubules to the blood[324]

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Stoppage of the renal arterial blood flow by compression, resulting in s of renal arterial pressure for short periods (1 to 3 minutes) causes

anuria but has no remarkable consequences for renal excretion (§8 6) during re-establishment of blood flow, except for some proteinuria and lipuria[720, 1099]. *Tying of the vena cava in rats above the entrance* of the renal veins causes only transient anuria, the blood finding its way back to the heart by abdominal veins which enlarge day by day[6] Elevation of the renal venous pressure in nembutalized dogs to 350 mm. of saline *proves oliguretic and oligochloruretic. Higher pressures* (550 mm. saline) decrease renal blood flow and glomerular filtration rate[127, 954].



[illegible]
cc. of water were given by stomach tube During the interval *B*, the animal was run around the laboratory. Uninterrupted line, right kidney, interrupted line, left kidney. Nerves are not needed for this inhibition of water diuresis which is presumably in part of postpituitary origin. After Klisiecki et al. [605]

9 14 *Exercise.* With strenuous exercise in operating an ergo or running, there is usually a reduction in urine flow and chl excretion, an inhibition of water diuresis (Fig 44) both during after the performance[70, 73, 248, 697], and an albuminuria[62] proportion to the intensity of the work. Mild exercise has no influe on water diuresis[513] The physiological relation between exerc and urine flow is not wholly clear although postpituitary mediation suspected[605] However, where pituitrin given with water lengthe the latent period of diuresis, shortens the diuresis, and reduces th amount of ingested water recovered, these effects are counteracted b exercise[73]

In prolonged exercise there is a loss of fluid from the plasma through sweating and possibly through passage into the muscles The uptake of water by muscles under certain experimental conditions[883] has long been considered to result from the formation of intracellular metabolic products whose effective osmotic pressure is greater than that of their precursors A simple osmotic interpretation of water uptake by muscles is not completely satisfactory[1168] but there is a correlation between increased osmotic pressure of the blood in exercise and inhibition of water diuresis[74] In exercise there is also a fall in filtration rate and renal plasma flow[70]

Information on the lyuretic effect (for ions) of exercise is conflicting except in the matter of chloride excretion which, it is agreed, is decreased[70, 503, 1147] This effect is not consistent with an interpretation of the inhibition of water diuresis in terms solely of the antidiuretic hormone of the neurohypophysis since there is commonly found a chloruresis in these antidiureses (§9 5)

9 15 *Dehydration* Other than by pituitary antidiuretic intervention which arises from relative rather than absolute dehydration and which cannot induce extreme oliguresis, the urinary flow is ordinarily decreased by water deficit to a small extent only[20] Urine flow is minimal through a wide range of dehydration (Fig 1) so that the degree of dehydration cannot be assessed from it However, anuria occurs with extreme dehydration perhaps reflecting a failure of the regulation to maintain adequate renal function

9 16 *Miscellaneous Antidiuretic Influences* A diminished diuretic ponse to water is found in severe salt deficiency (Fig 39)[59, 552, 747, 1143], in hypoproteinemic rats[293], during the first two days

of menstruation[509], in deficiencies of pantothenic acid or riboflavin[411, 414], and in instances of liver dysfunction[8] including that which follows a high fat diet[655, 971]. Urine formation in cirrhosis is often retarded, particularly after meals, a phenomenon designated as *opsiuria* by Gilbert and Lereboullet[427].

Oliguresis or oliguria is found during the breathing of atmospheres of low oxygen tension (5 to 12 per cent) by anesthetized dogs[1068, 1071, 1084], during continuous pressure breathing at 10 to 40 mm of mercury above ambient pressure in man[310], following laparotomy in the rabbit[523, 720], and as a result of administration of certain liver extracts[439, 1056] including ferritin[56]. Histamine, choline[783] (said not to act in dogs with an Eck fistula), heparin[1103], cinchoninic acid derivatives and antipyretics such as antipyrin, pyramidon, acetanilid, and phenacetin[53] are also to be grouped here. Urine, itself, containing antidiuretic material, behaves either antidiuretically on this account, or diuretically[674, 676] (§8.23, 10.2). Certain other influences such as sleep[859], posture[663, 664, 814, 1136], centrifugation[985], etc. are discussed in the previous chapter where the reverse effects are given.

9.17. *Hormones* The antidiuretic effects of hormones are discussed in Chapter X. Hormones possessing antidiuretic activity (Table XXV) include those of the adrenal medulla, pars nervosa, and pancreas (insulin).

CHAPTER X

ocrines in Urinary Function

rmones acting on diverse organs in concert present many and antagonisms, real and imaginary The physiologist pressure to profess a coherent science is fortunate to spe- function of some organ or system where hormonal influence y minimal Renal physiologists are not so fortunate. They v very well how hormones exert influence on the kidney, ough unique stimulation or depression of tubular or glo- s, through the process of their own excretion, through alter- concentrations of other substances presented for excretion, other extrarenal influences Neither do they know the full hich humoral effects depend on the presence or absence of nes And where hormones are regulators of renal function, know the degree to which the kidney regulates these regula- ndocrines make possible the urinary function of the kidney xists a substantial fund of information on this subject

The Posterior Pituitary

e Actions of Posterior Pituitary Extract or Pituitrin The posterior pituitary on renal activity was first noted to be lagnus and Schafer[705] injected a pituitary decoction into ized dog, producing a brief rise in blood pressure, a longer esis, and a still longer lasting oncometric expansion of the e diuretic effect of pituitary was later observed by many s[377, 379, 388, 515, 695, 699, 765, 807, 900, 915, 928, 1007,

a of certain types predisposes to the appearance of the ct while normal or unanesthetized animals usually show an effect[253, 557, 607, 1007] When large doses of pituitary given during a water diuresis, compared with smaller ones, are the less antidiuretic and have been regarded as relatively 7]. When pituitrin does act diuretically this is often an t, a more lasting antidiuretic effect being manifest later, uresis is usually associated with an increased excretion of ntidiuretic effect is more readily seen when initial rates of are high[984] as in water diuresis where the quantity of

excreted solids does not strictly govern the facultative urine volume. A diuretic effect is commonly seen where the urine, flowing slowly, is concentrated, and its increased flow is obligated to the extra elimination of solids brought on by pituitrin[1027, 1029]. Hence pituitrin is said to be diuretic for urines of high osmotic pressure and antidiuretic for urines of low osmotic pressure[514, 515]. The diuretic effect in anesthesia may be related to the low urine flow which often obtains in that state However, Nelson[806, 833] finds in morphine-urethanized rabbits rendered diuretic by isotonic sugar solutions that intravenous pituitrin gives a marked, if transient, diuresis

In unanesthetized man or in lightly anesthetized dogs intravenous injection of postpituitary extract may produce not a diuresis but rather an antidiuresis, and the blood pressure need not be elevated. This has suggested that the diuretic action of this material is associated with the pressor activity[695] Actually large doses of pressor principle which bring about circulatory disturbances are diuretic[379].

The antidiuretic action of pituitrin is usually considered the more significant physiologically. It occurs in the presence (for example, with nicotine antidiuresis) or absence of a pressor effect; and it is not annulled by vasodilators such as amyl nitrite, sodium nitrite, nitroglycerine, and papaverine[782] However, the pressor fraction (vasopressin, pitressin, postlobin-V), regardless of whether it manifests a pressor effect, is ordinarily responsible for the antidiuretic activity[378] When mixtures of pitressin with water or urine are dialyzed, both the pressor and antidiuretic activities disappear from the dialysis residue[309] First clearly recorded by von den Velden[1091] in normal subjects and in those with diabetes insipidus, the antidiuretic property of postpituitary was further established by Motzfeldt[794] It obtains in normal animals where the hormone acts directly on the kidneys[253, 888, 993],* and in dogs anesthetized with chloralose[559]. The antidiuretic activity has been reported less effective at high water loads than at low[497, 677] Lyuretic diuretics (glucose, sodium sulfate, sodium chloride, urea) and some xanthinoids (melamine, adenine, formoguanamine) prevent the antidiuretic effect; others like caffeine, *theobromine, or thyroid may or may not* *Uranium and cantharidin* polyurias are not reduced by pituitrin[782]. Parabiotic dogs[540], as well as isolated kidneys[184, 1092], respond antidiuretically. The antidiuretic action of pituitrin is not, therefore, simply consequent to

* The hypothesis of Molitor and Pick[784–786] that the antidiuretic principle of the hypophysis acts on a water center in the midbrain has received no support from other investigators and has been demonstrated to be fallacious by Theobald[1053]

delayed absorption of water from the gut, or due to excessive removal of water from the blood by the tissues[522, 993]. It occurs if water is given intravenously.

An antidiuretic factor (which may be different from pitressin) is excreted in the urine[431, 479, 491, 517, 524, 1104], can be assayed biologically[124, 198, 199, 479, 487, 568, 815, 929], and is said to be detectable in human blood[656, 733] It is adsorbed by blood and serum and by tissue extracts such as of muscle, brain, kidney, and particularly liver Blood and liver contain an enzyme-like substance which destroys pituitrin[524, 574]. Various cations, anions, and organic substances when added to posterior pituitary extracts prolong the antidiuresis obtained by subcutaneous injection Zinc, nickel, cadmium, and ferrocyanide are most active[815] This is said to account for high assays of antidiuretic substance obtained from blood and urine.

Harris[491], who has used both direct electrical stimulation of the neurohypophysis in the conscious rabbit and intravenous injection of postpituitary extract, finds the appearance of antidiuretic material in the urine in each case. This lends stronger support to the theory that this material is of pituitary origin than do negative results obtained from hypophysectomized animals subjected to dehydration[431, 562, §10.10] There is evidence that dehydration causes excretion of both pituitary and extrapituitary antidiuretic substances

10 3 *The Oxytocic and Pressor (Antidiuretic) Principles of the Postpituitary* The nature of the so-called diuretic principle of the postpituitary has been a matter of controversy. Melville and others[765, 1028] performed experiments on unanesthetized rabbits which were supposed to indicate that the diuretic effect of pituitary preparations including pressor and oxytocic factors is largely due to the pressor factor, the oxytocic constituent (oxytocin, pitocin, postlobin-O) probably exerting no diuretic influence However, Kuschinsky and Bundschuh[632] and Fraser[377–379] believed the oxytocic hormone to have a definite diuretic action in rats, whether hydrated or not, apparently not due to contaminating pressor (antidiuretic) hormone. Slight dehydration destroys the response to the oxytocic hormone, suggesting that its action is on excess water. Some physiological antagonism has been postulated to exist between the oxytocic and pressor hormones in water exchange in view of the belief that the antidiuretic factor also acts primarily on excess water[21]

Pressor extracts[379] appear to exert a diuretic action only in doses with drastic circulatory effects The increase in urine flow has been

thought to be basically a salt diuresis However, the oxytocic hormone may be extremely chloruretic[295, 632] and it is possible that the increased chloride excretion after pressor extract is actually due to contaminating oxytocic hormone.

Jones and Schlapp[574] find after intravenous injection of postpituitary extract that pressor and oxytocic activities of the circulating plasma disappear at the same rate, none remaining after 2 hours. Unexcreted portions of both oxytocic and pressor substances are destroyed in the body, possibly by the liver, kidney, and spleen, extracts of which are capable of destroying these corresponding activities The pressor and oxytocic principles exist in untreated press juice of posterior lobe in the form either of a single large molecule or two separate large molecules of similar sedimentation properties This large molecular species is considered the native hormone by Rosenfeld[914]. Its sedimentation constant is about one-third to one-half that of egg albumin Pituitrin, pitocin, and pitressin contain the active principles as cleavage products of much smaller molecular weight and less concentratable by ultracentrifuge Van Dyke et al [1081] have found a protein behaving like a homogeneous substance (mol wt, 31,000) in the ultracentrifuge, extractable from fresh posterior lobes of oxen, and possessing constant oxytocic, pressor, and antidiuretic properties About 11 micrograms of nitrogen of this protein is equivalent to 1 unit of U S P. reference standard

10 4. *The Quantities of Antidiuretic Hormone Inhibiting Water Diuresis.** When a fasting subject under standard conditions assumes the recumbent posture, a diuresis begins some 3 to 6 hours later, with abrupt onset and termination This diuresis, which can be inhibited by postpituitary extract, was ascribed by Hart and Verney[497] to a fall in the concentration of the antidiuretic substance of less than 1 part in 15 billion parts of plasma Partial inhibition of water diuresis occurred with intravenous injection of extract to the extent that the concentration of antidiuretic substance in plasma was much less than 1 part in 6 billion

For the rabbit, Levitt[656] states the minimal amount of pitressin which caused a definite and constant decrease in the urine output and increased the chloride concentration, as 0 00002 units Maximal anti-

* Heller[516] finds that mammalian pituitary bodies contain at least 8 times as much antidiuretic principle on the basis of body weight as the glands of any nonmammalian species A relation between the phylogenetic development of Henle's loop and the amounts of antidiuretic hormone is suggested.

diuresis results from 0 002 units per rabbit, giving a 100-fold range in dosage between the minimal and maximal effects Subminimal doses may have a slightly inhibiting effect on water diuresis without significantly affecting the chloride excretion

A graded diuresis in 10 to 15 kg dogs with diabetes insipidus, when normally hydrated, was obtained by Shannon[965] when 0 001 to 0 005 pressor units were injected per hour. This range is also physiologically active in normal animals In a 10 to 15 kg dog the normal rate of liberation of the antidiuretic hormone, therefore, is estimated as 0 001 to 0 005 units per hour

10 5 *Postpituitary and Solute Excretion* Adolph and Ericson[21] showed that pituitrin in man does not inhibit the excretion of solutes from ingested solutions, while it inhibits completely the extra excretion of water following ingestion of pure water It has little oliguretic effect on the obligatory urine flow With ingested salt solutions more concentrated than the maximum urinary concentration pituitrin does not prevent water excretion, and with certain solutions such as isotonic potassium chloride and isosmolar urea, solutes are allowed to escape with obligated water while excess water is held back Pituitrin appears to render the kidneys insensitive to an excess of water in the blood, helping thus to distinguish diuretic influences due to dilution from those due to salt excretion

Stehle and Bourne[1029], Unna and Walterskirchen[1077], Melville[764], and others find that pituitrin administration during obligatory urine formation increases the chloride output and the urine flow, the former independently of the effect on urine flow However, the quantity of urine put out depends on the salt content of the animal or its salt intake On a salt-poor diet there is little diuresis, but with salt-rich diets there is a notable increase in urine volume In any case the salt output increases In dogs with or without barbiturate anesthesia, the diuretic response to pituitary is greatly augmented by giving the animal salt prior to pituitary administration, although salt administration even without pituitrin might be expected to increase urine flow

Silvette[977] showed that increasingly concentrated salt solutions when injected into pituitary treated rats provoked correspondingly increased urine volumes As the dose of extract was reduced the chloride concentrating effect tended to disappear before the inhibitory influence on water excretion was affected. An increased excretion of water in extract-treated rats given isotonic saline was correlated with a low (1 per cent) "concentration ceiling" of the urine It was further

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of the respective principles on the urinary excretion of these electrolytes falls in with the antagonism hypothesis. Just as excess of cortical hormone is said to raise the threshold of retention for these ions, excess of postpituitary principle has been thought to lower it[298]. The actual demonstration of these changes in serum electrolyte as a result of pituitary excess has not yet been clearly set forth.

In normal dogs Spingarn, Mulinos, and Maculla[1020] find no effect of pitressin on plasma chloride concentration When normal dogs are subjected to intramuscular injections of pitressin tannate in oil, which has a longer lasting action than aqueous preparations, there is only a small alteration in the water exchange of the animal, since it normally does not drink an excess and concentrates its urine maximally. In water load the pitressin effect is seen in the absence of water diuresis but otherwise the only noticeable effects are moderate oligodipsia, some oliguresis, and baruria Urine flow was shown to decrease 8 to 30 per cent under pitressin while water intake decreased 8 to 40 per cent. Dogs put on this low level of intake, but without pitressin, become very thirsty; when on pitressin they do not The oligodipsia is consistent with a tendency for the plasma chloride to fall even though increased excretion of chloride takes place only in the first 24 hours of pitressin administration

No change in serum chloride following pituitary administration was observed by McIntyre and Van Dyke[756] in nephrectomized dogs, from which it was concluded that the extract acted only on the kidneys and not extrarenally But Buschke[204] reports an increase in nephrectomized rabbits and argues for an extrarenal, "tissue" action[296] of pituitrin.

Fromherz[388] found a fall in the blood chloride with large doses of pituitary extract, as did Britton and Kline[171] Gilman and Goodman[432] found that in rabbits a "pituitrin anemia" is produced through the retention of water which leads to lowered osmotic pressure of the serum and ultimate destruction of red cells

It is difficult to tell to what extent the antidiuretic and oxytocic factors operate individually in the regulation of salt levels in the plasma The problem is not made simpler by supposing that effects on salt are independent of effects on water Salt and water metabolism are physiologically never wholly independent so long as a threshold of retention for sodium and chloride exists Where an agent such as a cortical hormone or, as seems likely, a pituitary hormone is capable of altering a threshold of retention, the change induced implies no less than an altered excretion of either salt or water, both of which are factors of hreshold, or of the two Where the excretion of one factor, for

shown[976] that as the dosage of pituitary extract was reduced from high levels to zero in the presence of a small load of 0 2 per cent sodium chloride, water excretory function gradually increased while that of chloride steadily diminished. Water excretion approached normal more rapidly so that when urine excretion was inhibited only 11 per cent, chloride excretion was still 280 per cent above normal. Chloruresis here is thus more sensitive an indicator of postpituitary excess than antidiuresis.

In man Little et al [677] examined the effects of intramuscular pitressin. Subjects were either hydrated by several hours of steady water ingestion, or not hydrated prior to the administration of the pitressin Usually there was a decrease in the rate of water excretion following pitressin which was accompanied by either an increase or a decrease in the rate of chloride excretion. Occasionally there was an increase in urinary chloride concentration at the same time as an increase in urinary flow, reflecting definite chloruretic action The rate of water excretion was greater during the postpitressin period in hydrated than in nonhydrated subjects. Chloride excretion was inversely proportional to the preinjection rate of chloride excretion and was not related either to the preinjection chloride level in the serum or to the state of hydration of the subject.

McQuarrie, Thompson, and Ziegler[760] observed that with repeated doses of postpituitary extract the body weight could be made to increase 3 to 4 per cent in a few days. Upon withdrawal of the antidiuretic principle, when the diet was low in salt, there followed an ecuresis capable of removing edema. Sodium and chloride balances were negative both during the antidiuretic and the diuretic periods, while potassium, calcium, phosphorus, and nitrogen balances were little affected by the extract.* It is interesting to note that spontaneous diuresis occurred occasionally in spite of administration of extract.

10 6 *Excess of Postpituitary Principle in Relation to Serum Electrolyte.* In keeping with the idea that some antagonism exists between the actions of postpituitary antidiuretic substance (possibly admixed with oxytocic principle) and certain adrenal cortical principles[247, 984, §10 16], it might be supposed that the former in excess would tend to lower serum concentrations of sodium and chloride as the latter tends to raise them This belief is strengthened particularly since the actions

* Stehle[1027] reports the urine after pituitrin administration to be rich in potassium, calcium, magnesium, and phosphorus. Fraser[379] states that the oxytocic hormone depresses phosphorus excretion

which period the denervated neurohypophysis produces vasopressin, but after 3 to 10 days the activity of the pituicytes again disappears because of loss of trophic nerve influences This ushers in a "permanent phase" because the pituicytes now actually undergo degeneration.* O'Connor and Verney [820] showed how after about a week hypophysectomized dogs return from temporary polyuria to homaluria. Assessment of neurohypophyseal activity by measuring the emotional inhibi-

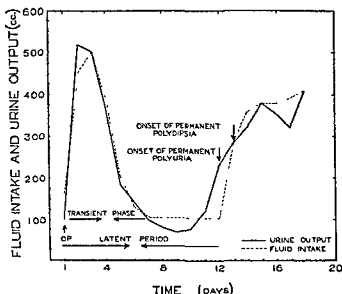


Fig 45. Course of the Polyuria and Polydipsia of a Typical Case of Experimental Diabetes Insipidus in the Cat *OP* indicates time of operation. Daily average for 6 weeks: fluid intake, 474 cc, urine output, 453 cc After Fisher et al [370]

tion of water diuresis (§10 18) indicated that 95 per cent had been abolished Presumably a remaining functional fragment of the pars nervosa restrains the excessive formation of urine

10 8 *The Primacy of Polyuria or Polydipsia.* Two cardinal signs of diabetes insipidus are polydipsia (or polyposia) and polyuria The more or less but not always simultaneous occurrence of these signs

*See Gersh and Brooks [421, 422] and Hickey et al. [543] on the correlation of physiological and cytological changes in the neurohypophysis in experimental diabetes insipidus.

example, water, is obligated to remain relatively constant to satisfy physiological pressures of other hormones, etc, the change in the one factor of the threshold, that is, sodium or chloride, may seem independent of the other. Such an appearance, however, is probably illusory.

10.7. *Diabetes Insipidus* * Diabetes insipidus is a disease prominently characterized by polydipsia, polyuria, and hydruria The ratio of water intake of animals with diabetes insipidus to water intake of normal animals is approximately the same in individuals of a given species, but the ratio varies among different species, for example, in the rat it is 7; in dog, 10 to 20; in man, 25 Richter[905] states the maximum voluntary intake of water in diabetes insipidus to be proportional to body weight in different species rather than to surface area as, it is said, is the case in normal animals But for mammals of diverse species Adolph[16] finds total water intake proportional to the 0 88 power of the body weight (§1 2) It is not possible here to set out any extended discussion of the presently conceived nature of the pituitary aberrations in diabetes insipidus but consideration of certain salient features are of interest in a study of the urinary function of the kidney.

Although the presence of the anterior lobe † has been considered necessary for the onset of a permanent diabetes insipidus[370, 484, 903], Heinbecker and White[512] state that a maximum and permanent diabetes insipidus follows removal or complete denervation of the entire neurohypophysis resulting in a retrograde degeneration of the entire supraoptic nuclei and the rostral ventral portions of the paraventricular nuclei In the act of denervation, failure to interrupt 15 per cent of the fibers innervating the neurohypophysis will prevent the development of permanent diabetes insipidus, and failure to interrupt smaller percentages of these fibers leaves increasing degrees of diabetes measured in terms of polyuric intensity. Complete interruption increases the urine output 10 to 20 times in the dog It is believed that at initial operation there is sufficient injury to vasopressin-forming tissue to prevent hormone secretion, leading to the so-called "transient phase" (Fig. 45) of polyuria A "normal interphase" follows during

* See Van Dyke[1079, 1080] and Geiling[417] on physiology and pharmacology of the pituitary body; Fisher, Ingram, and Ranson[370] for a critical review of the literature on diabetes insipidus; and Harris[490] on the neural control of the pituitary gland

† Following the Schafer-Herring hypothesis of the diuretic action of pituitary decoctions[928, § 10 2], Frank[375] believed diabetes insipidus to result from hyperfunction of the pars intermedia.

is balanced by intakes of water with little salt. Intake of water with salt can only aggravate thirst, the more as the ratio of the salt to the water is the higher.

10.9. *Tests for Diabetes Insipidus.* The urine in diabetes insipidus is usually dilute with respect to salt. With water deprivation it becomes somewhat concentrated[268, 288, 964, 1041], more so for substances like calcium and nitrogen than for chloride. A hypertonic urine can apparently be formed in the absence of the antidiuretic hormone of the pituitary. But such urine is difficultly obtained and this defection in renal function has, in one form or another, provided the basis for recognizing diabetes insipidus. When the disease is present the kidneys fail to concentrate the urine. Meyer[774] tested for diabetes insipidus by giving salt. White and Findley[1129] distinguish a nondiabetic polydipsia from that of diabetes insipidus by withholding water for 6 to 12 hours. Only in diabetes or renal disease (otherwise distinguishable) will polyuria persist. ... nondiabetic urine flow falls to normal and its concentration rises. ...n and Rynearson[179] find that a patient refraining from water ...ce long enough to induce extreme discomfort is not likely to have diabetes insipidus if at the end of this period the urinary specific gravity is greater than 1.010. Hare et al [488, 542] refined the application of these principles in testing whether a pre-existing "water diuresis" is inhibited by an injection of salt. If it is, the hypothalamico-hypophyseal system is said to be in good order; a continuation of the high rate of urine flow suggests that the polyuria is of pituitary origin. Again, under test conditions, diabetes insipidus is revealed by the fact that after a dose of hypertonic sodium chloride, the concentration ratio for chloride ordinarily remains less than 1, whereas in the normal subject, the concentration ratio rises above 1. The use of the ratio of the concentration of the chloride in reabsorbed fluid to the concentration of chloride in the plasma (R/P) for this test has little to recommend it, since the U/A ratio always varies in an inverse manner to the R/P, is simpler to determine, and requires no assumptions as to the magnitude of the glomerular filtration rate.

10.10. *Hypotheses Concerning Neurohypophyseal Regulation of Water Output.* Verney and his co-workers[605, 820, 1026, 1093, 1097, 1098] have propounded a useful physiological hypothesis to the effect that the regulation of water output in the urine is largely under the

In a sense there is little physiological profit gained in pursuing the idea that either polyuria or polydipsia is primary in diabetes insipidus. Polydipsia (excessive drinking) may be brought about by thirst, volition, or force, or as a result of psychiatric aberration [85]. Polydipsia (excessive thirst, excessive drinking), as we have noted (§§52, 64), is commonly associated with relative dehydration or elevated extracellular and intracellular electrolyte concentrations; and the degree of polyuria following on a given polydipsia depends in a complex way upon the salt intake [86, 1137]. Correspondingly, a loss of body fluid (sweating and otherwise) has a variable effect on the intake of water, depending on the quantity of salt lost with the fluid [21, §7.12]. Polyuria and polydipsia in diabetes insipidus are collaterals of the salt-water intake (and balance) ratio. When salt is restricted from the diet, the polyuria is reduced [86, 1141, 1137], whereas if dietary salt is increased, it may be enormously aggravated [92, 1143, 1142, 1044]. Swann [1142, 1144] showed how in diabetes insipidus in the rat the polyuria appears primary at some times while at others the polydipsia appears primary. Total nephrectomy prevents the polydipsia of both the transient and permanent phases of diabetes providing the animals are drinking water. If they are drinking saline, and if they have come to the permanent phase of the disease, nephrectomy does not abolish the polydipsia. This salt effect is relatively specific, being produced by sodium bicarbonate and Ringer's solution as well as by sodium chloride, but not by sodium sulfate, sodium citrate, potassium chloride, or calcium chloride. However, it cannot be implied that diabetes insipidus is merely a defect in sodium and chloride metabolism, otherwise simply limiting the intake of these would constitute the prime therapeutic in the disease. Furthermore, Winter, Ranson, and [illegible] [1138] have shown that in cats on a salt-free diet the polyuria following interruption of the supraopticohypophyseal tracts can be [illegible] whereas feeding cats on normal sodium chloride intakes [illegible] fall in urine volume.

If we acknowledge that salt-water disturbances are not alone in the pathogenesis of diabetes insipidus, and that serum concentrations of sodium chloride are either unaffected in the disease [86, 1135] or increased [91, 1141], it remains consistent with the greatest number of observations that thirst in diabetes insipidus, as under other conditions, is most closely associated with a relative rather than an absolute dehydration. This relative dehydration is not produced by polyuria, *per se*, but by hydruria, that is, by the failure to eliminate sodium and chloride in proportion to water. Loss of water with little salt tends to raise plasma electrolyte concentrations and induce thirst unless this effect

is balanced by intakes of water with little salt Intake of water with salt can only aggravate thirst, the more as the ratio of the salt to the water is the higher.

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The antidiuretic substance found in the urine of rats and dogs under conditions presumably calling for release of pituitary antidiuretic substance is thought by Arnold[49], Walker[1104], and Ham and Landis[479] not to originate necessarily from the postpituitary. Not only has antidiuretic material been obtained from the urine of hypophysectomized animals but that material apparently differs from pituitary substance in lacking the chloruretic property While commercial pituitrin passes through cellophane and is not concentrated by ultracentrifuge, the antidiuretic material in urine does not pass through cellophane and is concentrated by ultracentrifuge Ralli et al [881], however, find that the chloruretic activity of commercial pitressin is lost by dialysis although the antidiuretic potency remains Thus they argue that nonchloruretic, antidiuretic material may be of pituitary origin Harris[491] believes that dehydration causes excretion of two substances, pituitary and extrapituitary, because direct electrical stimulation of the neurohypophysis in unanesthetized rabbits causes excretion of less material which does not lose activity on dialysis than does dehydration, in which latter case the material loses some antidiuretic activity on dialysis Species differences, admittedly, may enter this picture.

A number of considerations bring into question the desirability of regarding water conservation as a primary pituitary function. First, since pituitarectomized cats and rats[1104] and dogs[964] respond to water ingestion by diuresis, and to water deprivation by oliguria, some mechanism other than postpituitary appears to regulate urinary water output. Even where a homaluric flow in dogs is maintained by constant intravenous infusion of antidiuretic hormone, water diuresis has been observed to follow water loading[965]. White et al [364, 1125, 1128, 1131] do not confirm the theoretical requisite of the hypovasopressinemia hypothesis that in diabetes insipidus the latent period * of water diuresis be reduced Indeed, there may be no clear cut water diuresis in this disease and patients may retain loaded water for at least 8 hours, suggesting some accessory mechanism at work Where decreased lag of elimination of water behind absorption of a second drink of water (ingested while a water load from a first drink persists or while urine flow is well above normal) could be taken as evidence of a lack of vasopressin in normal subjects, no such decreased lag is found[1125]

* The "latent period" of diuresis in terms of the Verney hypothesis[605] represents a period between intake of water and onset of augmentation of urine flow, supposed to depend primarily on the time required for preformed vasopressin to drop below its effective antidiuretic level in the blood (in turn a consequence of destruction and excretion of the hormone following cessation of its secretion). A latent period is present whether water is taken orally or parenterally.

an increase in osmotic pressure of the body fluids of less than 2 per cent. Urea in solution does not elicit the antidiuretic action presumably because it exerts little effective osmotic pressure. Dextrose, being somewhat permeable, does not produce osmotic stimulation so well as sodium chloride (Fig. 48). Solutions effective by internal carotid artery are ineffective by vein (small quantities)

Antidiuretic hormone is released from the pituitary by two agents, emotional stress (§9 8, 10 18) and raised osmotic pressure of body fluids The latter is conceived to stimulate cytons of the supraoptic and possibly of the paraventricular nuclei whose axons pass down the stalk to the pars nervosa (Fig. 46). Verney speculates that certain vesicles within the field of the supraoptic nucleus might be adapted for the osmoreceptive function Accordingly, the far-reaching effects of such stimulation would follow from the properties of a colony of membranes whose aggregate surface area is only of the order of 1 square millimeter[1098] Along these lines a water conservation "reflex" has been postulated to consist of osmoreceptors attached to afferent cells, an adjustor-efferen
hypophyseal nerve cells, and the
tors Raised osmotic pressure of
osmoreceptors and result reflexly in the release of antidiuretic hormone Presumably "normal" osmotic pressures exert a tonic influence toward the steady release of hormone, while low osmotic pressures are accompanied by reduction of hormone secretion

The "water conservation" aspect of postpituitary control of urine flow has been developed by Gilman and Goodman[431]. Ingram, Ladd, and Benbow[562], and others[215, 368, 486, 987] Rats, either dehydrated or given hypertonic sodium chloride orally, show an increased urinary excretion of material which resembles pituitary antidiuretic principle. It tends not to appear in the urine of hypophysectomized animals or of animals in water diuresis In support of the water conservation function of the pars nervosa are the findings of Simon[987], Hickey, Hare, and Hare[543], and Chambers[214] indicating that dehydration or salt administration in rats leads to a decrease in the antidiuretic and oxytocic content or potency in the pituitary glands of these animals Subcutaneous implantations of DCA pellets in rats produces increased fluid intake and increased urinary output of antidiuretic factor In normal rats drinking saline also produces these effects It is observed that output of antidiuretic factor in the urine is proportional to increased fluid intake no matter by which of these means produced[990] Some increased osmotic pressure of body fluids, however, may also be common to these increased fluid intakes

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However, Klisiecki et al [604, 605] state they have observed not only the earlier onset called for but an increased delay with dehydrated animals as well. White and Findley[1128] point out that a latent period is not peculiar to the excretion of water alone but is found with the *excretion of chloride and glucose* Since it is found with these and not with no-threshold substances such as creatinine, it is suggested that the latent period for water excretion is nonspecific and is simply characteristic of threshold substances Some lyuretic and specific diuretics have a latent period for action also *One may inquire what the nonpituitary* fraction of the latent period for a water diuresis might be, a matter not properly answered by tests in diabetes insipidus alone.

Second, Fee[357, 358] has observed typical water diuresis in decerebrate and decorticate dogs when morphine and nonvolatile anesthetics were avoided Newton and Smirk[813] further attest that in decerebrate cats with total hypophysectomy a natural control of water diuresis is present; there is the usual latent period, and a normal diuresis curve They conclude that the pituitary gland and that part of the brain above the tentorium, including the hypothalamus, are not indispensable parts of the mechanism controlling water diuresis Although Fisher, Ingram, and Ranson[370] have attempted to mollify the force of these experiments by intimating that unknown quantities of antidiuretic hormone *might have been released during operation and could act in* place of the hypophyseal structure, Pickford[854] grants that antidiuretic hormone alone is not to be considered the only factor limiting urine flow Further clarification is obviously desirable

Third, is any single mechanism of renal water regulation sufficient to care for the body economy? It is well known that the body readily permits itself extensive absolute dehydration or hydration so long as regulation of the concentrations of electrolytes in body fluids can be maintained (§6 5, 7 6) How much of the complex of salt-water balance is controllable by an antidiuretic hormone alone? When a prolonged infusion above the LIC is stopped, the lyuresis outlasts the diuresis (§8.9) This is not likely to reflect pituitary intermediation beginning at the time of cessation of fluid input.

Even if hypertonic salt solutions elicit the release of hormone in some proportion to their hypertonicity, that does not account for the fact that the output of water per unit load of solution varies complexly (not in proportion) with the tonicity[1170, 1173]. Per unit load, very dilute solutions of sodium chloride bring about high urine flows; solutions somewhat more and somewhat less concentrated than isotonic bring about small urine flows; and solutions increasingly hypertonic bring about increasing urine flows (Fig. 29). The idea that there is

an increasing "osmotic" diuretic effect with increasing hypertonicity, antagonizing the action of antidiuretic hormone cannot be supported either for sodium chloride solutions or for solutions of other substances such as potassium chloride or sodium sulfate. Isotonic solutions of the latter behave no differently than 5 per cent glucose by vein or pure water by mouth in their effect on urine flow[703, 1177, §7 18]. In the case of isotonic sodium sulfate, interstitial in its distribution[156], yet failing to behave diuretically as does isotonic sodium chloride, we have an important difficulty to be surmounted by the water conservation hypothesis of the neurohypophysis.

Fourth, hyponatremic states accompanied by lowered osmotic pressure of body fluids are not necessarily accompanied by polyuria[742, 743, 1098] as might be expected. Here Verney postulates "accommodation" of osmoreceptors to sustained reductions of osmotic pressure. It may be inquired if such accommodation can occur to sustained elevations of body fluid osmotic pressure. If it be conceived that thirst[1175] found in relative dehydration originates in osmoreceptors (§6 2), either specialized as vesicles or generalized in entire nerve or other cells, the lack of accommodation to the sensation of thirst[20] may have a bearing on this matter. In any case in salt deficiency there is not a normal water diuresis[552, 1143]. It is either absent, less than normal, or delayed longer than normal (Fig 39). The oliguria of water intoxication further indicates that qualifications must be made in describing renal water exchange by a postpituitary mechanism.

"Water conservation" can be expressed in complex ways. It is not enough to show that *without* the antidiuretic hormone water loss follows (and that, therefore, water is not conserved). In diabetes insipidus water intake readily replaces loss so that in steady states there is little observable alteration in the relative or absolute hydration of the organism. It is apparent that homeostasis of body volume and concentration is still possible even if water must be balanced at higher levels of intake and output. Excess of hormone "conserves" excess of water only, leading to relative hydration and distinctly injurious consequences for the organism. Normal hormonal secretion, if to it be attributed the initially low excretion rates for water found with loads of isotonic saline, "conserves" water only for a limited time since augmentation of the saline load ultimately results in sufficiently increased elimination of water (Fig 5) and salt to restore body volume to normal[1035]. If the hormonal secretion were shown to decrease or stop as saline loads become large, the fact of continuing volume (water) regulation would remain. This would emphasize that conservation as well as elimination can exist without the hormonal factor. Even though saline loads aggra-

vate the severity of diabetes insipidus, conservation of body water is still effected by compensatory adjustment of intake.

Lipschitz and Stokey[672] found that rats fed ecuretic (dehydrating) doses of sodium chloride excreted urinary antidiuretic hormone while rats receiving other ecuretic diuretics like melamine excreted only insignificant amounts of antidiuretic hormone in the urine. Dehydration by melamine, which is accompanied by considerable loss of salt, is ineffective in promoting hormonuria; repeated melamine diuresis on two successive days leads to a greater deficit of water than salt (relative and absolute dehydration) and thirst. Thirsting animals excrete moderate amounts of the antidiuretic hormone. Thus again, water conservation, per se, is not the crucial element in postpituitary secretion Rather does it seem to be osmotic stimulation.

It is not primarily to impugn the water conservation hypothesis that this discussion has been brought to bear. We are aware of the support which is given it from the evolutionary viewpoint (the development of the mammal, of its "need" for conserving water, of Henle's loop,* and the elaboration of the antidiuretic principle[516] in these species). Yet it is well to recognize that the idea of water conservation is a simplification by ellipsis and difficult to verify. Conservation of water by vasopressin is physiologically meaningless without colligated conservation of salt and the conjunctive action at least of other hormonal agents to regulate relative hydration and dehydration. If intake of water is stopped dehydration will follow, in part a result of urinary water loss, whether vasopressin is present or not. The essential difference is that the rate of development of dehydration is more rapid in the latter case. It is incontrovertible that the neurohypophysis regulates the rate of water exchange—but can we equate this fact to water conservation?

THE ANTERIOR PITUITARY

10.11 Crowe, Cushing, and Homans[257] first recognized a diuretic or polyuric function of the anterior pituitary or adenohypophysis, following experiments in which it was transplanted into hypophysectomized dogs Teel[1050] showed that anterior lobe extracts had diuretic potency, although a weak antidiuretic effect is mentioned by Motzfeldt[794] The anterior lobe, extracts of which increase renal blood flow and diodrast *Tm*[511] apparently exerts a trophic influence on the kidney. White et al.[1135] have found that growth hormone of the anterior pituitary, administered for 9 to 12 days in dogs, doubles paraaminohippurate and almost doubles inulin clearance. It also

* No longer considered essential to active water reabsorption[1124].

raises the depressed clearances in hypophysectomized animals to greater than normal values

Marked diuresis which occurs in normal dogs following administration of anterior pituitary[1131] but does not occur in thyroidectomized dogs[78] suggests that the diuresis results from thyroid stimulation[113, 593]. However, the thyroid normally does not exert a significant diuretic action nor is it required for diuresis. It appears more that the thyroid is necessary influence on urine flow. Thyroidectomy has no for the action of the diuretic principle of the anterior pituitary rather than that it mediates the diuretic effect of that lobe[369]. Thyroidectomized and thyroidectomized-hypophysectomized dogs fail to respond diuretically to anterior lobe administration unless accompanied by thyroid, which latter alone is insufficient to affect the water exchange[1130]. The increased urine flow caused by occlusion of the pituitary stalk[706] is abolished by thyroidectomy and restored by giving thyroid gland.

After complete destruction of the hypophysis and hypothalamus there does not develop the characteristic polyuria of diabetes insipidus which follows removal of the posterior lobe alone, or an appropriate neural lesion[157], and diabetes insipidus can be eliminated by complete hypophysectomy[594]. Total removal of the pituitary gland in rats tends to produce only a temporary diabetes insipidus in most, and a "permanent" diabetes in none. Richter[903] believes that the degree of diabetes insipidus depends on the amount of anterior lobe remaining whether or not this lobe is still in connection with the pituitary stalk, that is, it is needed in the production of the disease. Anterior pituitary extract will consistently restore diabetes insipidus which has lessened in severity in long term hypophysectomized rats to its maximal postoperative levels[951]. Removal of the anterior lobe or of the complete hypophysis, that is, leaving or not the posterior lobe, decreases water diuresis[221] and prevents the diuretic action of yohimbine[389, §9.3].

Heinbecker and White[512] do not believe the anterior lobe is necessary for permanent diabetes insipidus. They point out that maximum and permanent diabetes insipidus follows removal or complete denervation of the entire neurohypophysis in dogs, resulting in retrograde degeneration of the entire supraoptic nuclei and the rostral ventral portions of the paraventricular nuclei (§10.7). Pickford and Ritchie [856] employed several types of operation to study the hypothalamic-pituitary control of water excretion in dogs, removal of posterior lobe alone, section of supraoptic tracts, attempted removal of anterior lobe alone, simple hypophysectomy (removal of both lobes and some stalk), and simple hypophysectomy and section of supraoptic tracts at

the same time After any operation involving loss of the anterior pituitary the diuretic response to water was diminished and was not restored by thyroid administration or that of anterior pituitary and cortical extract. Diuretic response to saline tended to be greater than that to water Polyuria might follow any of these operations even in the absence of the anterior lobe, but only after section of the supraoptic tracts was it of fairly long duration.

Thus the action of the anterior pituitary is not settled. Peters[842] observes that it may be necessary to determine how far the reputed effect of the anterior lobe derives from its ability to overcome cachexia Gaebler[394] states the primary effect of anterior pituitary to be on water metabolism and storage, and secondarily on diuresis. And Smith[999] cautions against thinking of the anterior pituitary as providing a diuretic principle in view of the widespread participation of this endocrine gland in the regulation of other glandular and metabolic functions and of the uncertainty of the effects of these extracts upon salt and water equilibria We cannot certainly state that the anterior pituitary "participates in a positive rather than permissive manner in ordinary diuresis and in diabetes insipidus, or that it acts in opposition to the antidiuretic principle of the posterior portion of the gland"

The Thyroid

10 12. Eppinger[345] discovered that the administration of thyroid had diuretic and ecuretic effects in man and was able to remove certain types of renal and cardiac edema Thyroid will induce diuresis in normal dogs[301] and in rabbits which have been starved and deprived of water[390]. It may also bring on chloruresis[347]. Pancreatectomy abolishes thyroid diuresis in otherwise normal animals[301] as does dministration of pituitrin or ergotamine[347]. Luminal and light hloretone narcosis in rabbits inhibit thyroxin diuresis while paraldehyde nd deep chloretone narcosis augment it In cats[877] there is no gnificant diuretic effect of thyroid feeding although some oligolyuresis f chloride is evidenced Rats excrete large volumes of urine low in hloride in hyperthyroidism[408]

It is believed that the elevation in metabolic rate produced by thyroid r thyroxin is not responsible for the diuretic effect[131]. Dix, Rogoff, nd Barnes[301] found elevated rates in pancreatectomized dogs which o not respond to thyroid administration with diuresis White, Heinecker, and Robinson[1133], Findley[363], and Bruhn[181, 182] conrm this in finding that a dose of dinitroorthocresol or dinitrophenol, hich increases metabolic rate much as thyroid, is not diuretic nor does

it increase water exchange. The effects of thyroxin on urine flow (Fig. 49), metabolism, and water exchange (increased) are consistent with the belief that its action results from increasing the quantity of solute requiring renal excretion, but the fact that metabolism-raising agents

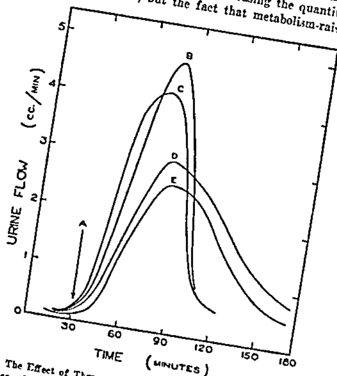


Fig. 49. The Effect of Thyroxin on the Course of Water Diuresis in a Dog At *A*, 250 cc of water were given by stomach tube *E* = mean of 6 responses before the giving of thyroxin. *B* = mean of 4 responses while the animal was under the influence of thyroxin *D* = mean of 3 responses obtained at a minimum of 8 days after the last injection of thyroxin. *C* = mean of 5 responses while the animal was again under the influence of thyroxin Thyroxin increases the intensity and diminishes the duration of water diuresis After Klisiecki et al [603].

other than thyroid are not diuretic makes this interpretation less than completely satisfactory In man hyperthyroidism is only occasionally evidenced by increased urine flow [956].

Claims that the thyroid hormone or thyroxin has a specific action on urine flow have not been substantiated fully [843] but there is evidence that such action occurs. Gaunt, Cordsen, and Liling [412] found that

this procedure. They believe the effect of thyroidectomy in relieving these diabetic polyurias is proportional to the residual amount of vasopressin-forming tissue.

The Adrenal Cortex

10 14 *Adrenal-Renal Insufficiency.* Marshall and Davis[722] were the first to show that extirpation of the adrenal glands led to a type of renal insufficiency in cats characterized by an impairment of urea excretion They noted no difference in the handling of salt by the kidneys Baumann and Kurland[85], Marine and Baumann[715], and Zwemer[1189] called attention to the fact that after adrenalectomy there was a fall in the plasma concentration of sodium and of chloride, and that the ultimately fatal effects of this operation could be palliated by administration of sodium salts and water, with prolongation of life. Loeb and others[681, 684] indicated that in addition to characteristic decreases in sodium and chloride levels there was an increase in serum potassium concentration, and they drew attention to the fact that these changes in adrenalectomy were similar to those found in Addison's disease.

Cortical insufficiency affects the excretion of sodium and chloride by the kidneys, apparently lowering the tubular reabsorption of these ions and their thresholds of retention Sodium may be excreted in appreciable quantities in the urine of the dog at plasma levels as low as 106 mEq /l. (where normal is ca 145), chloride at levels as low as 85 mEq /l. (where normal is ca. 108) [496]. In the opossum and marmot adrenalectomy leads to increase in serum sodium and chloride values over normal preoperative values, that is, the opposite of dog and cat There is a correspondingly subnormal urinary excretion of salt[983]

In the adrenalectomized dog there are reduced creatinine and urea clearances These appear to result chiefly from loss of sodium chloride, replacement of which restores renal function almost, but not quite, to normal[492]. Cortical extract restores normal function In adrenalectomized dogs whose renal function is maintained in good condition on a high sodium-low potassium intake, the MUC for chloride has been reported to fall to 199 mEq /l compared to 306 mEq /l in normal dogs under comparable conditions The ability of the kidneys to concentrate, as measured by specific gravity tests, is similarly reduced in the adrenalectomized dog although the ability to dilute the urine, at least with respect to chloride, is almost unimpaired[616] No significant histological changes referable to cortical insufficiency are detectable in the kidney[423]

in rats with full fledged hyperthyroidism there is an increased diuretic response to water and a marked resistance to water intoxication In these animals there is less chloride loss than usual in water diuresis and the protective action of thyroid against water intoxication is thought to be based on salt retention, possibly in part through the increased adrenal cortical activity in hyperthyroidism. Brull[186] further demonstrated that the diuretic effect of thyroxin is due at least in part to direct renal action Kidneys originating from thyroxinized dogs, when transplanted simultaneously with control kidneys to a donor, were found to secrete more rapidly and to give larger responses to saline infusions and to hypophysectomy than controls

In hypothyroidism diuresis and water intoxication following water load behave as in normal animals

10 13. *Endocrine Interrelations with Thyroid.* Gaunt[408] and others[412] find that the protective effect of hyperthyroidism against water intoxication is largely abolished by adrenalectomy, but the intense cortical stimulation by thyroxin probably does not account for all of the effects on water metabolism Diuresis in hyperthyroid-adrenalectomized rats is much like that in untreated adrenalectomized animals. Water is absorbed from the intestine more rapidly in the former case though less rapidly than in normals.

Thyroid is synergistic with anterior pituitary in producing diuresis[113, 363, 1133, §10 11]. Biasotti[113] originally supposed that the thyroid gland constituted a necessary intermediary for the diuretic action of extract of anterior hypophysis because he found that the diuretic effect of such extract was missing in thyroidectomized dogs However, the thyroid normally exerts no diuretic action

In cats and dogs thyroid administration increases the severity of diabetes insipidus[369] as does thyroxin or anterior pituitary extract[181, 877] Thyroidectomy may relieve the disease or make it more responsive to pitressin but is not more therapeutically effective than a low salt diet[363]. Mahoney and Sheehan[706], by occluding the pituitary stalk of dogs with a silver clip, showed that the subsequent polyuria and polydipsia could likewise be abolished by total thyroidectomy and restored by thyroid gland administration, whereas total thyroidectomy alone had no effect on daily fluid intake and output White, Heinbecker, and Robinson[1133] found that the transient polyurias of hypophysectomy are usually immediately abolished by thyroidectomy while the high and permanent polyurias of complete hypophysectomy, including pars tuberalis and median eminence, may be unaffected by

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Commonly in adrenalectomized animals there is, in addition to a loss of plasma sodium and chloride, a compensatory increase in potassium which may leave the osmotic pressure of the plasma almost unchanged[506]. Usually, however, there is a decrease in the osmotic pressure of the plasma which results in a shift of water from extracellular to intracellular spaces. For this reason and also because fluid enters the red cells, increasing their volume relative to the plasma volume[416, 428], there tends to be hemoconcentration There is also an increased plasma specific gravity, a fall in blood pressure, and a sensitivity to hemorrhage The kidneys excrete more chloride and sodium than normally (since these are relatively concentrated in the urine even at somewhat elevated urine flows, there is a tendency to isosthenuria) and there is, conversely, a reduced capacity to concentrate potassium. Either polyuria, homaluria, or oliguria can obtain[93, 415, 492, 982] but there is little water diuresis in response to water load and sodium lyuresis in response to sodium load is diminished[913]. Birnie et al.[124] find in the serum of normal rats a labile antidiuretic and chloruretic substance which increases after adrenalectomy but is not found in the blood of hypophysectomized rats. This substance may in part account for the failure of water diuresis after adrenalectomy

McCance[742] compares experimentally induced salt deficiency (Table XXIV) and Addison's disease. These conditions are similar in loss of weight, poor water diuresis[59, 552], and low serum sodium and chloride. They differ in that little change is found in serum potassium in salt deficiency, but then this is not a necessary accompaniment of Addison's disease A normal blood pressure in salt deficiency is contrasted with a low pressure in Addison's disease Other conditions which may simulate adrenal insufficiency in regard to water diuresis include certain cardiac, liver, and renal diseases, and pantothenic acid and riboflavin deficiencies[411].

The renal aberrations brought on by cortical insufficiency, as in Addison's disease, have been utilized in testing for the presence of this condition It is not always possible to distinguish cortical insufficiency from normalcy on the basis of differences in serum levels of sodium, potassium, or chloride because these values are not necessarily altered significantly in the change from one state to the other. If a patient suspected of Addison's disease is deprived of salt, however, the serum values of sodium and chloride tend to be lower than normal Also whereas non-Addisonian urine, formed during salt deprivation, tends to show extremely low U/A ratios for these ions, in Addison's disease concentration ratios tend to be close to unity[270, 271].

A less dangerous test for cortical insufficiency as in Addison's

disease than provoking exaggerated changes in serum electrolytes is found in the procedures of Robinson, Power, and Kepler[911]. Based on the fact that in cortical insufficiency the kidneys do not respond to a water load with the usual diuresis, a standard water load is established by drinking 20 cc/kg. If any single hourly volume of urine following morning drinking is greater than the volume of the night urine, the test is negative, that is, the water diuresis is sufficient to rule out cortical insufficiency If the hourly volume is less than the night volume, the test is tentatively positive in that Addison's disease may or may not be present Further testing is based on the fact that the diseased state tends to be accompanied by a relatively lowered concentration ratio for urea, a relatively raised concentration ratio for chloride, and a relatively diminished water diuresis Arbitrarily the product

$$\frac{U_{urea}}{A_{urea}} \cdot \frac{A_{Cl}}{U_{Cl}} \cdot \frac{\text{maximum hourly volume of day urine}}{\text{volume of night urine}}$$

should be greater than 30 (urine concentrations are for night sample) in patients with no cortical insufficiency When the product is less than 25, Addison's disease is probably present if certain few, possibly mistaken conditions are ruled out, for example, nephritis, diabetes insipidus, some dehydration Since in Addison's disease and in adrenalectomized animals there is impaired renal function[387, 492, 1047] tests to reveal nephritis in these conditions must be chosen critically.

Under certain standard conditions the concentration of sodium and chloride in sweat is 15 to 60 mEq/l. Conn[236] finds that desoxycorticosterone and adrenocorticotrophic hormone cause these levels to fall Untreated patients with Addison's disease show sweat concentrations of 75 to 115 mEq/l for these ions. These findings have been suggested as a basis for assaying the activity of the desoxy-like corticosteroids Of singular interest is the fact that these hormones act with much the same effect on such discrete structures as the sweat glands and the renal tubules, to the same metabolic end, namely, altering the electrolyte concentration of the plasma Leaf and Couter[651] propose that normal conservation of body sodium by variation in renal excretion is actually the result of increased cortical activity in response to low sodium intake, and vice versa

Thorn et al [1066] have devised a test for adrenal cortical insufficiency based on the differing response in this condition as compared with that of the normal, following a single dose (25 mg) of purified pituitary adrenocorticotrophic hormone. In normal men there is

a decrease in circulating eosinophils and a rise in uric acid excretion relative to that of creatinine. In insufficiency the normal response fails to occur. This test appears primarily to measure adrenal cortical reserve of hormones regulating the metabolism of carbohydrate, fat, and protein

10.15. *Effects of Excess of Adrenal Cortical Hormones.* In normal subjects intravenous injections of cortical hormone over a brief period result in a decreased renal excretion of sodium, chloride, and water[1061, 1064]. Calcium, magnesium, and nitrogen are not affected If administration of desoxycorticosterone esters is in sufficient quantity and continued for longer periods, there is positive water balance with marked edema, hypoproteinemia, and cardiac insufficiency[280, 361, 627]. Even in patients with Addison's disease, excessive hormone therapy is potentially as dangerous as in normal individuals. Withdrawal of hormone is accompanied by sodium lyuresis, potassium antilyuresis, and loss of weight. In dogs under excessive (toxic) dosage with DCA, serum sodium and chloride rise, serum potassium falls, and attacks of paralysis occur which can be alleviated by intravenous or oral potassium chloride.

When DCA is first administered to a normal animal there is a temporary period of retention of water as well as sodium and chloride After several weeks of hormone administration, excretion and intake of water is augmented. A daily urine volume in dogs in excess of 2500 cc is common and 4000 cc has been exceeded. This condition was called by Loeb and others[627, 878] a kind of "diabetes insipidus," superficially on account of the polydipsia and polyuria The disturbance in water balance gradually disappears and normal weight returns[683]. Thirst is considered the "primary" feature of this syndrome, first because pituitrin is relatively ineffective against the polyuria, and second, because fluid restriction does not lead rapidly to dehydration as in true diabetes insipidus However, the polydipsia may be secondary to the relative dehydration of high plasma sodium concentration which latter is induced in part by altered kidney activity. Thus the polyuria following polydipsia[1047] could still be regarded as a "primary" renal feature. The matter of primacy is much as complicated here as for diabetes insipidus (§10 8).

Excessive administration of DCA can lead to edema in animals[682] and in man However, in normal men on daily DCA injections the increase in body weight and plasma volume is enhanced in some proportion to the quantity of salt in the diet[227]. In young rats maintained on isotonic saline, the immediate effect of DCA is a rise in fluid intake. This is followed by a regression of intake values toward control

levels[459].* Excess of cortical extract differs in its effect on plasma volume from excess of DCA[1047]. Whereas the former will restore the low plasma volume of the adrenalectomized animal or the Addisonian patient to normal, it will not raise it above normal. DCA, however, will raise plasma volume above normal in these instances as well as in normal human subjects.

Apparently not all cortical steroids acting on salt-water metabolism have similar effects In rats, cortical extract enhances urine flow in the presence of either a positive or negative water load DCA will act diuretically also except when water is in deficit[830]. Thorn, Engel, and Lewis[1065] found that 17-hydroxycorticosterone and 11-dehydro-17-hydroxycorticosterone lead to negative sodium and chloride balances in the normal dog, as opposed to desoxycorticosterone and corticosterone whose administration produces positive balances Langley and Clarke[644] showed that exposure of rats to high altitude (20,000 feet) brings on adrenal hypertrophy within 2 days This can be prevented by administration of cortical extract The fact that normal dogs at high altitude showed a lyuresis of sodium, chloride, and potassium and that this lyuresis of sodium and chloride did not occur after adrenalectomy, led these workers to favor the view of Thorn, Engel, and Lewis that certain fractions of the cortex cause increased excretion of sodium, in contrast to those causing retention It is suggested that under anoxic stimulation, certain components of whole extract are secreted independently of others (§8 26).

10 16. *Endocrine Interrelations with the Adrenal Cortex* An antagonism between the antidiuretic pituitary and the diuretic adrenal cortical hormones was postulated by Silvette and Britton[247, 984], Winter and Ingram[563, 1155], and others[913]. In the rat evidence of an antagonism is seen following removal of both pituitary and adrenal glands whereupon there is no immediate polyuria and polydipsia as is the case with hypophysectomy alone In removal of either or both glands there is an initial reduction in urinary chloride concentration, and postpituitary extract restores this concentration to normal; adrenal cortical hormone does not restore the concentration except in adrenalectomized rats In a few days urinary concentration returns to normal The immediate effect of hypophysoadrenalectomy is accounted for by the release of the kidney from the antidiuretic hormone whereupon the more slowly metabolized cortical hormone continues to act

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* The alterations in fluid exchange, etc following subcutaneous implantation of DCA pellets are reduced to minor values when pellets are implanted intrasplenically In the rat, DCA is apparently "detoxified" in the liver

a decrease in circulating eosinophils and a rise in uric acid excretion relative to that of creatinine. In insufficiency the normal response fails to occur. This test appears primarily to measure adrenal cortical reserve of hormones regulating the metabolism of carbohydrate, fat, and protein

10.15. *Effects of Excess of Adrenal Cortical Hormones.* In normal subjects *intravenous injections of cortical hormone over a brief period* result in a decreased renal excretion of sodium, chloride, and water[1061, 1064]. Calcium, magnesium, and nitrogen are not affected. If administration of desoxycorticosterone esters is in sufficient quantity and continued for longer periods, there is positive water balance with marked edema, hypoproteinemia, and cardiac insufficiency[280, 361, 627]. Even in patients with Addison's disease, excessive hormone therapy is potentially as dangerous as in normal individuals. Withdrawal of hormone is accompanied by sodium lyuresis, potassium antilyuresis, and loss of weight. In dogs under excessive (toxic) dosage with DCA, serum sodium and chloride rise, serum potassium falls, and attacks of paralysis occur which can be alleviated by intravenous or oral potassium chloride.

When DCA is first administered to a normal animal there is a temporary period of retention of water as well as sodium and chloride After several weeks of hormone administration, excretion and intake of water is augmented. A daily urine volume in dogs in excess of 2500 cc is common and 4000 cc. has been exceeded. This condition was called by Loeb and others[627, 878] a kind of "diabetes insipidus," superficially on account of the polydipsia and polyuria. The disturbance in water balance gradually disappears and normal weight returns[683]. Thirst is considered the "primary" feature of this syndrome, first because pituitrin is relatively ineffective against the polyuria, and second, because fluid restriction does not lead rapidly to dehydration as in true diabetes insipidus However, the polydipsia may be secondary to the relative dehydration of high plasma sodium concentration which *latter is induced in part by altered kidney activity.* Thus the polyuria following polydipsia[1047] could still be regarded as a "primary" renal feature The matter of primacy is much as complicated here as for diabetes insipidus (§10 8).

Excessive administration of DCA can lead to edema in animals[682] and in man However, in normal men on daily DCA injections the *increase in body weight and plasma volume is enhanced in some proportion to the quantity of salt in the diet*[227]. In young rats maintained on isotonic saline, the immediate effect of DCA is a rise in fluid intake. This is followed by a regression of intake values toward control

1017. *Water Balance and Cortical Hormones* In adrenalectomized dogs the amount of fluid lost as urine above the total fluid intake is inadequate to account for the dehydration and associated changes of insufficiency. A much greater loss over intake occurs during recovery following injections of cortical hormones A normal dog deprived of food and water can lose more fluid and maintain good condition than can the adrenalectomized dog The adrenalectomized animal may put out more or less urine than normal but since it invariably takes in less food and water, the ratio of fluid output to total fluid intake is always greater, giving negative water balance[1046] When replacement hormone is given to an adrenalectomized dog, blood volume and pressure rise and the dog eliminates far more fluid in the urine in relation to the total intake than during insufficiency. A large source of this fluid is provided by the tissues which had previously taken it up osmotically, on that account causing a partial water lack in other compartments

It is not superfluous to emphasize again that intake and output, at least of water and salt, must always be considered together in evaluating the significance of a polyuria or an oliguria for the water balance. Thus, with excessive administration of cortical hormone, despite an augmented urine flow, there can be a positive water balance or emuresis[361, 627] In cortical insufficiency, even if urine output is decreased, there can be a negative water balance or ecuresis Polyuria may be present in rats following adrenalectomy but its degree is to a large extent dependent on the dietary salt intake[93]

After adrenalectomy animals show not only diminution in water diuresis but increased susceptibility to water intoxication, an excellent measure of which, in rats, is the fall in body temperature[409, 410]. Although there is a demonstrable delay in the intestinal absorption of water in these animals, and a decreased emptying time of the stomach, these are only minor causes of failure in the excretion of administered water[973] The greatest portion of the administered water is retained in the body after absorption due to failure of renal elimination Cortical extracts, conversely, have a protective action against the onset of water intoxication consistent[352, 1045], but not necessarily associated, with their salt retaining properties[412]

The Adrenal Medulla

1018 *Actions of Epinephrine.* Administration of epinephrine to frog, cat, rabbit, and dog can give rise either to a diuretic or to an antidiuretic effect, small doses apparently favoring the former and

Further evidence of antagonism is seen in that there is no consistent or marked decrease in the sodium or chloride concentration of serum after adrenalectomy in cats with diabetes insipidus, as there is in normals; and adrenalectomy in cats with diabetes insipidus results in a rapid decline in water exchange. The fluid intake falls more than the urine output and negative water balance is set up[563]. Even if the urine output terminally exceeds the normal, there is a suppression of fluid intake The occurrence of diabetes insipidus with adrenalectomy reduces survival time but the total loss of water in negative water balance is not sufficient in itself to cause death Withholding fluid from otherwise normal diabetic cats causes greater total loss of water without fatality. Perhaps in double gland deficiency of this type the added loss of fluid from the extracellular to the intracellular space contributes to the morbidity

A series of other studies attests to the existence of some antagonism between postpituitary and adrenal cortex[124, 171, 246, 575, 797, 957, 1019, 1156, 1158]. After adrenalectomy there is an increased sensitivity to the antidiuretic action of pitressin. Under the influence of DCA administration rats drink more water and urine flow is increased while urinary chloride is reduced in concentration and amount. The reverse is true after postpituitary injection The diuretic effect of DCA is more pronounced in the hypophysectomized rat than in the normal. Normal dogs receiving DCA develop what resembles a very mild diabetes insipidus only partially controlled by pitressin (larger doses being required to reduce water exchange than in normal dogs) and aggravated by increased intake of nitrogen and salt. The specific gravity of the urine is low as in a hyposthenuria There may be an enuresis despite the polyuria, because of excessive polydipsia. Large doses of postpituitary extract administered to dogs twice daily for one to two weeks do not affect water intake and urinary output much but urinary sodium and chloride concentrations increase greatly and serum levels fall. Excess of pituitary extract has been reported to cause negative salt balance[760, 977] It is as if postpituitary excess resembled adrenal insufficiency in the reverse of the way that excess of cortical hormone resembles postpituitary insufficiency (diabetes insipidus) [171]. However, the extended hypothesis that the polyuria of diabetes insipidus is due to the unrestrained activity of the adrenal cortex is still unproved[1156]

Cortical hormone may act synergistically with anterior pituitary in restoring diabetes insipidus in hypophysectomized animals[575].

become explicable in terms of increased sympathetic activity inhibiting in varying degrees the secretion of the pars nervosa The relative roles of epinephrine and the renal nerves in the rapid inhibition were not elucidated Verney[1098] has ruled out increased blood pressure in the carotid sinus following epinephrine as a factor, favoring a specific interference in the chain of chemical reactions initiated in the nervous system by the faradic stimulus and ending in the release of vasopressin.

Medullectomy (demedullation of the adrenals) in rats, which gives rise to no symptoms of cortical deficiency, may or may not result in diminished water diuresis[413, 1031]. Where abnormally low urinary excretion after a single test dose of water is found, the normal response is restored by epinephrine In normal rats epinephrine greatly augments the polyuria of steady state, forced water intake, and partly counteracts the antidiuretic effects of pitressin It enhances the excretion of chlorides in both normal and medullectomized rats and does not prevent water intoxication although it can supplement the action of DCA *in restoring water diuresis to adrenalectomized rats* Gaunt, Liling, and Cordsen[413] do not believe that epinephrine plays any important role in ordinary water diuresis, the effects of overdoses in normal animals not being considered physiological

In narcotized dogs, epinephrine has been found to increase lymph flow while decreasing urine flow, so that in some instances lymph flows were the larger[937]

Other Hormones

10 19 *The Liver Hepatodiuretin* The liver has been thought to act on renal water excretion in at least two ways Molitor and Pick[781] suggested that it acts first to store incoming water of the body and then to release it gradually to the blood, accounting for some of the delay in the onset of water diuresis following a dose of water Second, it has been supposed to liberate a diuretic hormone or one which prevents the formation of edema Water diuresis after water load was found by these workers to begin in about 20 to 30 minutes in dogs with an Eck fistula * The diuresis curve rose more steeply and a water load was removed faster than in the normal dog whose latent period for diuresis was longer (50 to 60 minutes)

With an Eck fistula in dogs there is usually a lasting increase in voluntary water intake and output[255] up to 800 per cent although

* The Eck fistula allows portal blood to flow directly into the vena cava and excludes it from the liver whose blood supply then becomes wholly arterial and probably reduced to one quarter or one third of the normal combined portal and arterial flow

larger doses the latter[251, 269, 899–901, 1069, 1163]. In man the inhibition of urine flow is inconstant[68]. These effects are correlated with the observation and belief that small doses of epinephrine tend to constrict the efferent glomerular vessels producing a rise in intraglomerular pressure, while larger doses bring about constriction of afferent glomerular arterioles as well as efferent; both reduce renal blood flow. In man[68, 1002], doses which reduce renal blood flow may not greatly alter the inulin clearance so that the filtration fraction is increased Where epinephrine induces diuresis, Toth[1070] suggests the glomerulus is necessary for the effect. Intravenous injections in the puffer *(Spheroides maculatus)*, which possesses glomerular kidneys, result in polyuria. In the toadfish *(Opsanus tau)*, which possesses aglomerular kidneys, there is no significant diuresis

The demonstration of the dual nature of adrenal medullary hormone by Goldenberg et al.[441] is of interest in regard to the variable response of the kidney to this hormone. In addition to epinephrine, a primarily vasodilator material whose effect in elevating blood pressure is largely cardiac, the adrenal gland secretes perhaps 18 per cent nor-epinephrine (nor-adrenaline, arterenol), a primarily vasoconstrictor material. In man epinephrine blocks the vasoconstrictor action of nor-epinephrine when given in equal doses

O'Connor and Verney[821] studied the effect of increased activity of the sympathetic system in the inhibition of water diuresis by emotional stress in normal dogs (§9.8). In testing the effect of emotional stress (produced by 30 to 60 seconds of subcutaneous faradic stimulation) during water diuresis, they found two types of inhibition: a *rapid* one which was abolished by "denervation" (section of the splanchnics and denervation of the kidneys and adrenals); and a *slow* one due to release of antidiuretic substance from the posterior lobe of the pituitary. After "denervation" all tests showed slow inhibition which, however, could be prevented by the injection of epinephrine just before application of the faradic stimulus Epinephrine did not diminish the inhibition caused by injected postpituitary extract. It was therefore concluded that after the injection of epinephrine there was a failure to release the pituitary antidiuretic substance rather than a failure of this substance to act on the kidney. Removal of the pituitary gland abolished the slow inhibition and left the rapid one, the latter being thought due to vasoconstriction in that it resembled the effect following compression of a renal artery. After both removal of the pituitary and denervation, the two components of inhibition practically disappeared. The irregular appearance of slow inhibition during emotional stress in dogs with intact sympathetic systems may

Testosterone, excess of which readily brings on kidney hypertrophy resembling that caused by large doses of vitamin A[121], has no influence on diuresis[957]. In the dog it decreases the renal excretion of sodium and chloride, along with progesterone, estrone, and alpha-

TABLE XXV

Influence of hormones or glandular extracts, taken one at a time, on urine flow. + = increases; 0 = no change; — = decreases See text for details and qualifications

Hormone or Related Humor	Quantity	Urine Flow
Vasopressin, pressor or antidiuretic principle of posterior pituitary, pitressin	Large excess Small excess Deficit	+ → — — +
Oxytocin, oxytocic principle of posterior pituitary, pitocin	Excess	+
Anterior pituitary	Excess	+
Thyroid, thyroxin	Excess Deficit	+ 0
Adrenal cortical extract, desoxycorticosterone	Excess Deficit	+ —, 0, +
Epinephrine	Large excess Small excess Deficit	— + 0
Testosterone, progesterone, estrone, alpha estradiol	Excess	0
Insulin	Excess Deficit	+, — +
Hepatodiuretin	Excess Deficit	+ —
Ferritin	Excess	—

estradiol[1063], and decreases the urinary excretion of nitrogen and potassium[1121]. In this it differs, so far as potassium is concerned, from cortical hormone[597] In the rat testosterone is said to increase water and chloride excretion[634] or to have no significant effect on these[609]. Crystalline sex hormones have been observed to cause reduced urinary output when sodium output is reduced[1067] for an initial period of 3 days, after which there was a rebound and increased

in the ninth postoperative month it can fall to 200 per cent Chloroform poisoning has effects similar to those of the Eck fistula, but a dummy Eck operation, splanchnic section, or bile duct ligation is without effect The increased water exchange is correlated with greater dilution of plasma chloride after water is taken. This has been considered secondary to the diminution of the water storage activity of the liver whereupon there is prompt elimination of water and a reappearance of thirst

Heller and Smirk[521] deny the effectiveness of the "water storage" function of the liver since following alimentary absorption of water which is well in advance of diuresis, the rate of urine formation is not proportional to the then existing degree of hydration in muscle, liver, and blood. The degree of liver storage is considered by them to be insufficient to concern the delay in diuresis which follows administration of water. Another argument against the water storage function is the fact that the latent period of water diuresis is not markedly different for oral and intravenous water (5 per cent glucose). The latter might be expected to show the Eck-type latent period The Verney postpituitary hypothesis seems better, if not completely, to account for the latent period of water diuresis (§8.37, 10 10).

The status of "liver hormones" affecting renal function is not clear. Glaubach and Molitor[439] noted that liver extracts acting subcutaneously or intravenously may be antidiuretic or diuretic The diuretic factor or "hormone," *hepatodiuretin*, has been discussed by Pick[849, 850] and Oettel[825] and is said to be chloruretic, azuretic, and ecuretic (§8 17) *Antidiuretic material in liver extract has been* found by Theobald and White[1056], Ham and Landis[479], and Baez, Mazur, and Shorr[56] The latter identify their material as ferritin.

Liver function supposedly can be impaired other than in its "water storage" function, namely, in its hormone-producing function Shay, Kolm, and Fels[971] found that rats on a high fat diet retain more from a given quantity of water than do normally fed animals, a fact which might be explained by liver dysfunction brought on by the high fat diet. In hepatic disease, there is diminished water diuresis (§9 16)

10 20 *Insulin, Sex Hormones, and Others.* Insulin excess has variously been reported as diuretic or antidiuretic in some normal human subjects[298, 613], or antidiuretic in dogs[1098]. The antidiuretic effect is said to be of the pituitary type, the fall in urine flow being accompanied by a rise in the concentration of urinary chloride Insulin deficit is ecuretic and lyuretic[51].

Appendix

LIST OF MAIN SYMBOLS AND FORMULAS USED SYSTEMATICALLY IN TEXT

A: generally, concentration of a substance in plasma or blood; specifically, concentration in renal arterial plasma or blood

a: rate of plasma or blood flow in renal artery

A_T: threshold concentration (of retention)

B: body weight (grams).

b: volume of distribution

C: clearance ($=uU/A$)

cr: creatinine

$D_{4°}^{T°}$: specific gravity (relative density), the ratio of the weight of any volume of fluid at T° C to the weight of an equal volume of water at 4° C

DCA: desoxycorticosterone acetate

e: base of natural logarithms ($=2\ 731828$)

g: glomerular filtration rate

gl: glucose

I: concentration of a substance in intake fluid

i: rate of fluid intake as by intravenous infusion or drink

in: inulin.

L: load of a substance, absolute excess with respect to normal body content

LC: "leakage" or minimal concentration of a substance in the urine

LIC: limiting isorrheic concentration.

LIQ: limiting isorrheic quantity

ln: natural logarithm.

MIC: minimal isorrheic concentration

MIQ: minimal isorrheic quantity

MUC: maximum urinary concentration.

NLIC: nonlimiting isorrheic concentration

NLIQ: nonlimiting isorrheic quantity

PAH: paraaminohippurate

PSP: phenolsulfonphthalein, phenol red

Q_N: quantity of water required to restore isotonicity of body fluids

Q_r: quantity of water required to restore body fluid concentration (effective, osmolal) to that at the thirst threshold.

R: concentration of a substance in plasma or blood of the renal vein

r: rate of plasma or blood flow in renal vein

sodium excretion The female sex cycle is associated with premenstrual emuresis and menstrual ecuresis[1062]. Theelin is toxic to adrenalectomized rats and produces a conspicuous diuresis[415].

The effects of sex hormones, of parathyroid[753, §7 20], or of the putative hormones of the liver and intestinal mucosa[38, 39, 249, 250] are at present too ill defined to weave into any pattern of urinary function. Though specific effects of these have been suggested, as on "water metabolism," on "sodium excretion," or on "potassium retention," we may be fairly certain that they are neither pure nor simple Physiologists have yet to clarify these, to discover the significance of species and sex differences, and to integrate the disarrayed "facts" which now clog the literature.

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T: rate of tubular reabsorption (or secretion).
t: time.
Tm: maximum rate of tubular reabsorption (or secretion).
U: concentration of a substance in urine
u: rate of urine flow.
uU: rate of urinary excretion of a substance.
U/A: concentration ratio.
V_e: extracellular volume
V_i: intracellular volume.
W: osmotic work; total body water.
w: rate of extrarenal (or insensible) water loss.
x: a given substance.
y: a given substance.
γ: velocity constant of excretion (min^{-1}); rate of excretion of a substance per minute per unit load ($=\overline{uU}/\overline{L}$).
Δ: freezing point depression in degrees C.
ΔF: change in free energy.
τ: thirst threshold expressed as relative cellular water deficit.

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